After the discovery that several popular medicines may have harmed tens of thousands of people, experts are hunting for better ways to monitor drugs on the market

Gaps in the Safety Net

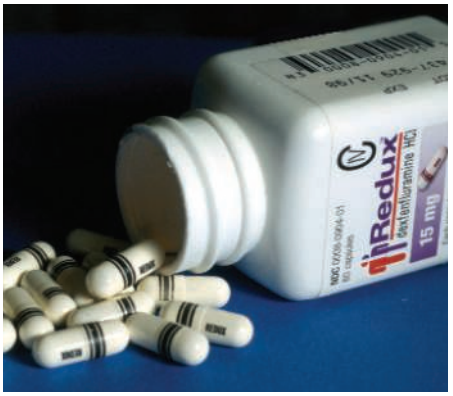
For those who trust government-approved drugs, 2004 was not a banner year. Merck, the maker of the anti-inflammatory medicine Vioxx, pulled the drug off the global market in September after a clinical trial linked it to heart attacks and strokes. In October, U.S. regulators concluded that a class of antidepressants can trigger suicidal thoughts in children and stepped up warnings of this danger. In December, studies of Celebrex, another arthritis medication, pointed to more cardiac risks. Just 5 days before Christmas, scientists running an Alzheimer's prevention study announced that Aleve, approved as a nonprescription painkiller in 1991, may also trigger heart problems.

These cases all involved drugs that had gone through extensive safety testing and had been on the market for years. And they raised disturbing questions: Should public authorities like the U.S. Food and Drug Administration (FDA) rethink what they consider acceptable risk? Should they move more aggressively to monitor approved drugs and restrict their use when problems surface among a fraction of patients?

The crises of 2004, some observers say, could trigger a shakeup in how drugs on the market are monitored. "I would like to believe that Vioxx could do for this decade what thalidomide did for the 1960s," says Jerry Avorn, a pharmacoepidemiologist at Harvard Medical School in Boston and author of the book *Powerful Medicine: The Benefits, Risks, and Costs of Prescription Drugs.* In the 1950s and 1960s, women in 46 countries who took thalidomide for morning sickness gave birth to more than 8000 children with severe abnormalities. Governments worldwide passed legislation requiring meticulous safety tests before a drug could be approved.

Judging by the numbers, the Vioxx case should elicit at least as strong a response. David Graham, an FDA drug safety officer, says it may have caused 100,000 heart attacks and strokes, a third of them fatal. Regulators from France to New Zealand had nervously discussed "signals" hinting at harm caused by the drug before 2004 but were unable to nail down their suspicions. It took a company-sponsored clinical trial to accomplish that (*Science*, 15 October 2004, p. 384).

Since the Vioxx debacle, officials running postmarketing surveillance systems are considering how they might do better. The uncomfortable truth, some say, is that all such systems have gaps. Several nations and the European Union (E.U.) boast aggressive surveillance systems, but many are new and have not been rigorously tested. "Everybody's in bad shape here," says Bert Leufkens, a pharmacoepidemiologist at the University of Utrecht in the Netherlands and an adviser to the Dutch and European Union drug agencies.



Same pill, different policies. FDA approved the diet drug dexfenfluramine, marketed as Redux, as European nations restricted access to it.

No public system is under greater pressure than FDA. Some members of Congress want to change it. Senator Charles Grassley (R–IA) plans to introduce legislation early this year to make FDA's existing Office of Drug Safety (ODS)—which is responsible for tracking the safety of drugs once they reach the market—independent of the drug approval mechanism in the Center for Drug Evaluation and Research (CDER), where ODS now resides. Academics and a few industry people say ODS needs a stronger legal mandate and more funds—but to make this happen, they must persuade a White House and Republican Congress that has traditionally recoiled from hands-on drug regulation.

Postmarketing surveillance systems, however, run on more than a legal mandate. Some of the strongest critics of the U.S. approach, like Avorn, say that FDA has all the police power it needs; it just needs to apply it creatively.

Risk tolerance

Forty years ago, European countries seemed relatively relaxed about drug approvals in contrast to FDA, which had earned a reputation for caution. Europe released thalidomide onto the market in the late 1950s, for example, and left it there for years. But an FDA reviewer spotted potential problems; she declined to let thalidomide through, and it was not approved.

Today, the roles are often reversed: FDA is frequently the first to approve drugs. The FDA staff is paid in part by "user fees" from regulated companies. Industry and patient groups lobby for speedy decisions, and FDA now turns some applications around in 6 months.

FDA has allowed greater risks in recent years than some other regulatory agencies, according to observers such as Lucien Abenhaim, a pharmacoepidemiologist at the University of Paris and McGill University in Montreal, Canada. He recalls getting little attention when he flew to Washington, D.C., in 1995 to warn FDA about life-threatening heart and lung ailments associated with the diet drug duo fenfluramine and dexfenfluramine (fen-phen). A recent study Abenhaim led had suggested that they increased cardiopulmonary risks up to 23-fold; European governments responded by limiting access to them. But FDA approved dexfenfluramine "without proper warning," says Abenhaim, only to see the drugs withdrawn in haste a year later after more than 100 people developed cardiopulmonary abnormalities.

Critics also fault FDA for its handling of the diabetes drug Rezulin. Two months after approving it in 1997, U.K. regulators pulled it off the British market because of concerns about liver failure. FDA read a different risk-benefit calculus in the data. "Most every country on Earth pulled the drug 2 full years before the FDA did," says Avorn.

Graham, a career FDA employee, claims that pressure to move faster has made CDER a "factory" for approving new drugs. Graham recently made headlines when he asserted in a Senate hearing that consumers "are virtually defenseless" against a repeat of the Vioxx affair. He said in a later interview that "my experience with FDA has been that

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they don't have the will" to go after drugs with safety issues. Graham says ODS, where he works, is often shunted aside because its views on a particular drug may threaten the judgment of FDA officials who allowed that drug on the market.

In an e-mail, FDA's press office declined to make senior officials available to answer questions for this article.

Shy gorilla?

Despite its woes, FDA remains a world leader in some areas—suggesting, perhaps, how tough it can be to police approved medications. "In many ways, the FDA is better able than we are at the moment to support independent research relating to pharmcovigilance," says Panos Tsintis, head of pharmacovigilance, safety, and efficacy at the 25-member European Medicines Agency (EMEA), the E.U.'s London-based drug approval and surveillance agency formed in 1995. Abenhaim praises FDA for its expertise but thinks these talents are poorly applied to postmarketing surveillance. He attributes this to government policy that gives FDA little authority to aggressively track and test marketed drugs.

Like agencies in many industrialized countries, FDA has two methods of conducting postmarketing surveillance. One is to commission specific studies. The other is to gather spontaneous reports of adverse effects in a database called MedWatch. Britain's drug regulatory agency claims to have the "world's largest computerized database of anonymized patient records," the General Practice Research Database (www.gprd.com). It's a fantastic research tool, says professor of medicine policy Joe Collier of St. George's Hospital Medical School in London—if you have a specific question and can pay. Full access to GPRD costs $600,000 a year.

No system is without flaws. One weakness of FDA's MedWatch, notes drug safety expert Alastair Wood, associate dean at Vanderbilt University in Nashville, Tennessee, is that it only skims the surface. He estimates that the 22,000 adverse events that are reported to the database each year represent only 3% to 10% of those experienced by patients. And the source could be biased: More than 90% of the reports come from companies, which are required to hand over reports given them by doctors, and fewer than 10% from doctors directly, FDA says.

Furthermore, FDA's MedWatch is isolated from patient care. In parts of Europe, "pharmacovigilance" offices are housed in hospitals, and physicians can wander down the hall to report adverse events. "It's not … an office somewhere in [FDA] with 8000 people collecting data," says Leufkens.

Then there's New Zealand's Medsafe, which employs 10 people on a budget of under $1 million to oversee more than 10,000 drugs on the market. Seventy percent of adverse-event reports to Medsafe come from general practitioners, 20% from hospitals, and 10% from companies. Those who submit reports can expect to hear from a Medsafe employee who's hunting for additional details. According to the World Health Organization, New Zealand's reporting rate on drug adverse effects is among the top three worldwide, says Stewart Jessamine, a Medsafe spokesperson.

New Zealand's challenge is very different from FDA's: The country has just 5000 prescribers and 3.5 million people. That makes it both easier to staff an interactive surveillance network and tougher to detect signals from dangerous drugs because fewer people are ingesting them, says Jessamine. Medsafe was watching Vioxx, for example, but officials could only conclude that "there's something happening, but we don't know what it is," he says.

This reflects the glaring limitation of even the best event-based reporting system: Doctors only report rare ailments that are easily linked to a drug. Vioxx and the heart attacks it induced are a different story altogether. "The doctor says … Mr. Blogg died from a heart attack, but he was 80, he did have angina and high blood pressure," says Jessamine.

No confidence. FDA's David Graham says the agency's system for protecting consumers from unsafe drugs is "broken."

Active surveillance

There are few ways to detect common but deadly hazards. One is through a clinical trial, like the one that brought down Vioxx. Another is by means of an epidemiology study that relies on massive databases, the kind maintained by HMOs such as Kaiser Permanente or government-funded health plans like Medicaid. Even though studies using these databases are cheap compared to clinical trials, running about half a million dollars, not many agencies fund them, says Brian Strom, a biostatistician and epidemiologist at the University of Pennsylvania in Philadelphia. Results from epidemiology studies sometimes carry less weight than those from clinical trials: Graham spent

Investing in Surveillance

	Total Staff	Postmarketing Staff	2004 Budget	Postmarketing budget
FDA-CDER (U.S.)	1800	94	$486 million	$24 million
EMEA (European Union)	300	55	$130 million	not available
Netherlands	130	25	$23 million	$3.5 million
New Zealand	50	10	$4.5 million	$900,000
United Kingdom	823	63	$125 million	$6 million

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3 years working with Kaiser in California on an epidemiology study of Vioxx and came to much the same conclusions as Merck eventually did, but his findings didn't prompt action against the drug.

FDA generally relies on companies to run postmarketing trials, called phase IV studies, often requesting them as a condition for a drug's approval. But follow-through is poor, a failing some blame on insufficient funds and others on a reluctance to confront drug companies. An FDA analysis released in 2003 found that more than 50% of phase IV studies don't even get started. FDA officials have said they need congressional authority to force companies to complete such studies.

Graham and Avorn think FDA has more muscle than its officials admit. If the FDA chief announced publicly that "there's a signal from Vioxx, the company's not responding," says Avorn, "the mere threat would have been enough" to force a clinical trial. The remedy, he and others say, is to give the drug safety office more clout.

Senator Grassley is proposing that the office remain within FDA but be distinct from CDER—a structure similar to that of the U.K.'s Medicines and Healthcare Products Regulatory Agency, in which safety regulators don't mingle with those who approve drugs.

Acting CDER chief Stephen Galson and other senior FDA officials declined to comment on FDA's postmarketing surveillance. But Jane Henney, FDA commissioner from 1998 until 2001 and now senior vice president and provost for health affairs at the University of Cincinnati, disagrees with Graham that FDA puts safety on the back burner, although she acknowledges that there will always be disagreement about how to handle drug risks. "As long as I was at the agency, the office of safety had a strong voice at the table," she says. Henney attributes FDA hesitancy to a simple problem: lack of resources. "We made a number of requests" to both Congress and the White House for increases in postmarketing surveillance funding, she says. Proposed changes included expanding FDA's access to large HMO databases to get a better grasp on adverse drug reactions and investing in research to more nimbly detect hints of drug problems. "Unfortunately, we just never got the money," says Henney.

Today, FDA devotes 5% of CDER funds, about $24 million, to the center's drug safety office, a fraction on par with the United Kingdom but proportionally lower than some other countries (see table, p. 197). Experts in both the United States and Europe believe that their countries should earmark far more money for postmarketing surveillance.

But money works best when melded with creativity. Even if FDA's drug safety office is refurbished, pressing postmarketing studies into action could mean flexing muscles drug regulators aren't accustomed to exercising.

Amid some controversy, France launched a new surveillance program several years ago that was spurred by the approval of Vioxx and Celebrex. EMEA had approved the drugs across Europe, but Abenhaim, then France's director general of health, wasn't convinced they worked as well as promised. He requested that a 2-year study of 40,000 people on Vioxx, Celebrex, or traditional nonsteroidal anti-inflammatory drugs begin before allowing France's national health care system to reimburse for the drugs. Abenhaim's position provoked an outcry, and he was asked to explain his position to the country's national ethics committee. In the end, the study was done. Since then, 50 more drug studies have been ordered. But, says Abenhaim, "there is still a lot of reluctance." Nor is the system efficient: The Vioxx study, for example, has not yet been released.

The Netherlands is eyeing a similar surveillance framework, says Leufkens. Meanwhile, EMEA, eager to harmonize drug approvals in Europe, will launch its own system in November 2005 to compel studies, using punishments such as financial penalties, says Tsintis.

The greatest worry of those pressing hardest for change, particularly in the United States, is that even thousands of possible deaths due to Vioxx won't prompt an overhaul of postmarketing drug surveillance. "My fear," says Avorn, "is that we will not be able to take advantage of this moment." —JENNIFER COUZIN

Radiation Hazards

Kyrgyzstan's Race to Stabilize Buried Ponds of Uranium Waste

With help from the West, local experts are devising ways to head off a potential landslide of Soviet-era mine tailings

MAILUU-SUU, KYRGYZSTAN—Alexander Meleshko scrambles up a terraced hillside, skirting tons of gravel laid to buttress the slope. All seems quiet on a cool day in late autumn, but Meleshko, a geologist with Kyrgyzstan's Ministry of Ecology and Emergency Situations (MEES), knows that this tranquil setting in the southwestern corner of the country is a disaster waiting to happen. Looming above is a 250-meter-high sandstone ridge rippled with shades of brown, yellow, and ochre. In front, entombed in an artificial hill, are 115,000 cubic meters of slurry chock-full of radioactive metals—enough to fill a football stadium. The noxious cocktail includes isotopes of thorium, copper, arsenic, selenium, lead, nickel, zinc, radium, and uranium. Meleshko, decked out in Army fatigues, stamps a foot on the soil. "There's more than 10,000 microroentgens per hour of radioactivity under here," he says—roughly 1000 times the local background rate.

High anxiety. Alexander Meleshko has charted a heightened landslide risk for Mailuu-Suu.

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All that protects Meleshko and the surrounding region from the tailings in this impoundment (called T-3), a leftover of Soviet-era uranium mining, is a meter-thick layer of clay. Experts have identified T-3 as a far-reaching threat: In the scariest scenario, the ridge could dissolve in a landslide, sweeping the tailings into the nearby Mailuu-Suu River. That's a chilling possibility. The Mailuu-Suu is a tributary of the Syr Darya River, the main source of irrigation water for the 6 million residents of the densely populated Fergana Valley. "It's a huge potential danger," says Vyacheslav Aparin, a senior scientist with the Complex Geological-Ecological Expedition in Tashkent, Uzbekistan. The valley, which extends southwest into neighboring Uzbekistan and Tajikistan, is a melting pot of peoples and beliefs, including enclaves of Islamic fundamentalists. A radioactive accident here could be traumatic to a region already simmering with tension.

The risk of a catastrophe is rising. Heavy spring rains in recent years have made landslides a more frequent occurrence in mountainous Kyrgyzstan, and in this seismically active

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