How a New Policy Led to Seven Deadly Drugs

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For most of its history, the United States Food and Drug Administration approved new prescription medicines at a grudging pace, paying daily homage to the physician's creed, "First, do no harm."

Then in the early 1990s, the demand for AIDS drugs changed the political climate. Congress told the FDA to work closely with pharmaceutical firms in getting new medicines to market more swiftly. President Clinton urged FDA leaders to trust industry as "partners, not adversaries."

The FDA achieved its new goals, but now the human cost is becoming clear.

Seven drugs approved since 1993 have been withdrawn after reports of deaths and severe side effects. A two-year Los Angeles Times investigation has found that the FDA approved each of those drugs while disregarding danger signs or blunt warnings from its own specialists. Then, after receiving reports of significant harm to patients, the agency was slow to seek withdrawals.

According to "adverse-event" reports filed with the FDA, the seven drugs were cited as suspects in 1,002 deaths. Because the deaths are reported by doctors, hospitals and others on a voluntary basis, the true number of fatalities could be far higher, according to epidemiologists.

An adverse-event report does not prove that a drug caused a death; other factors, such as preexisting disease, could play a role. But the reports are regarded by public health officials as the most reliable early warnings of danger.

The FDA's performance was tracked through an examination of thousands of pages of government documents, other data obtained under the Freedom of Information Act and interviews with more than 60 present and former agency officials.

The seven drugs were not needed to save lives. One was for heartburn. Another was a diet pill. A third was a painkiller. All told, six of the medicines were never proved to offer lifesaving benefits, and the seventh, an antibiotic, was ultimately judged unnecessary because other, safer antibiotics were available.

The seven are among hundreds of new drugs approved since 1993, a period during which the FDA has become known more for its speed than its caution. In 1988, only 4% of new drugs introduced into the world market were approved first by the FDA. In 1998, the FDA's first-in-the-world approvals spiked to 66%. The drug companies' batting average in getting new drugs approved also climbed. By the end of the 1990s, the FDA was approving more than 80% of the industry's applications for new products, compared with about 60% at the beginning of the decade.

And the companies have prospered: The seven unsuccessful drugs alone generated U.S. sales exceeding $5 billion before they were withdrawn.

Once the world's unrivaled safety leader, the FDA was the last to withdraw several new drugs in the late 1990s that were banned by health authorities in Europe.

"This track record is totally unacceptable," said Dr. Curt D. Furberg, a professor of public health sciences at Wake Forest University. "The patients are the ones paying the price. They're the ones developing all the side effects, fatal and non-fatal. Someone has to speak up for them."

The FDA's faster and more lenient approach helped supply pharmacy shelves with scores of new remedies. But it has also yielded these fatal missteps, according to the documents and interviews:

* Only 10 months ago, FDA administrators dismissed one of its medical officer's emphatic warnings and approved Lotronex, a drug for treating irritable bowel syndrome. Lotronex has been linked to five deaths, the removal of a patient's colon and other bowel surgeries. It was pulled off the market on Nov. 28.

* The diet pill Redux, approved in April 1996 despite an advisory committee's vote against it, was withdrawn in September 1997 after heart-valve damage was detected in patients put on the drug. The FDA later received reports identifying Redux as a suspect in 123 deaths.

* The antibiotic Raxar was approved in November 1997 in the face of evidence that it may have caused several fatal heart-rhythm disruptions in clinical studies. FDA officials chose to exclude any mention of the deaths from the drug's label. The maker of the pill withdrew it in October 1999. Raxar was cited as a suspect in the deaths of 13 patients.

* The blood pressure medication Posicor was approved in June 1997 despite findings by FDA specialists that it might fatally disrupt heart rhythm and interact with certain other drugs, posing potentially severe risk. Posicor was withdrawn one year later; reports cited it as a suspect in 100 deaths.

* The painkiller Duract was approved in July 1997 after FDA medical officers warned repeatedly of the drug's liver toxicity. Senior officials sided with the manufacturer in softening the label's warning of the liver threat. The drug was withdrawn 11 months later. By late 1998, the FDA had received voluntary reports citing Duract as a suspect in 68 deaths, including 17 that involved liver failure.

* The diabetes drug Rezulin was approved in January 1997 over a medical officer's detailed opposition and was withdrawn this March after the agency had linked 91 liver failures to the pill. Reports cite Rezulin as a suspect in 391 deaths.

* The nighttime heartburn drug Propulsid was approved in 1993 despite evidence that it caused heart-rhythm disorders. The officials who approved the drug failed to consult the agency's own cardiac specialists about the signs of danger. The drug was taken out of pharmacies in July after scores of confirmed heart-rhythm deaths. Overall, Propulsid has been cited as a suspect in 302 deaths.

The FDA's handling of Propulsid put children at risk.

The agency never warned doctors not to administer the drug to infants or other children even though eight youngsters given Propulsid in clinical studies had died. Pediatricians prescribed it widely for infants afflicted with gastric reflux, a common digestive disorder.

Parents and their doctors had no way of knowing that the FDA, in August 1996, had found Propulsid to be "not approvable" for children.

"We never knew that," said Jeffrey A. Englebrick, a heavy-equipment welder in Shawnee, Kan., whose 3-month-old son, Scott, died on Oct. 28, 1997, after taking Propulsid. "To me, that means they took my kid as a guinea pig to see if it would work."

By the time the drug was pulled, the FDA had received reports of 24 deaths of children under age 6 who were given Propulsid. By then the drug had generated U.S. sales of $2.5 billion for Johnson & Johnson Co.

Questions also surround the recent approvals of other compounds that remain on the market, including a new flu drug called Relenza. In February of 1999, an FDA advisory committee concluded that Relenza had not been proved safe and effective. The agency nevertheless approved it. Following the deaths of seven patients, the FDA in January issued a "public health advisory" to doctors.

A 'Lost Compass'

A total of 10 drugs have been pulled from the market in just the past three years for safety reasons, including three pills that were approved before the shift that took hold in 1993. Never before has the FDA overseen the withdrawals of so many drugs in such a short time. More than 22 million Americans--about 10% of the nation's adult population--took those drugs.

With many of the drugs, the FDA used tiny-print warnings or recommendations in package labeling as a way to justify approvals or stave off withdrawals. In other instances, the agency has withheld safety information from labels that physicians say would call into question the use of the product.

Present and former FDA specialists said the regulatory decisions of senior officials have clashed with the agency's central obligation, under law, to "protect the public health by ensuring . . . that drugs are safe and effective."

"They've lost their compass and they forget who it is that they are ultimately serving," said Dr. Lemuel A. Moye, a University of Texas School of Public Health physician who served from 1995 to 1999 on an FDA advisory committee. "Unfortunately the public pays for this, because the public believes that the FDA is watching the door, that they are the sentry."

The FDA's shift is felt directly in the private practice of medicine, said Dr. William L. Isley, a Kansas City, Mo., diabetes specialist. He implored the agency to reassess Rezulin three years ago after a patient he treated suffered liver failure taking the pill.

"FDA used to serve a purpose," Isley said. "A doctor could feel sure that a drug he was prescribing was as safe as possible. Now you wonder what kind of evaluation has been done, and what's been swept under the rug."

FDA officials said that they have tried conscientiously to weigh benefits versus risks in deciding whether to approve new drugs. They noted that many doctors and patients complain when a drug is withdrawn.

"All drugs have risks; most of them have serious risks," said Dr. Janet Woodcock, director of the FDA's drug review center. She added that some of the withdrawn

drugs were "very valuable, even if not lifesaving, and their removal from the market represents a loss, even if a necessary one."

Once a drug is proved effective and safe, Woodcock said, the FDA depends on doctors "to take into account the risks, to read the label. . . . We have to rely on the practitioner community to be the learned intermediary. That's why drugs are prescription drugs."

In a May 12, 1999, article co-authored with FDA colleagues and published by the Journal of the American Medical Assn., Woodcock said, "The FDA and the community are willing to take greater safety risks due to the serious nature of the [illnesses] being treated."

Compared to the volume of new drugs approved, they wrote, the number of recent withdrawals "is particularly reassuring."

However, agency specialists point out that both approvals and withdrawals are controlled by Woodcock and her administrators. When they consider a withdrawal, they face the unpleasant prospect of repudiating their original decision to approve.

Woodcock, 52, received her medical degree at Northwestern University and is a board-certified internist. She alluded in a recent interview to the difficulty she feels in rejecting a proposed drug that might cost a company $150 million or more to develop. She also acknowledged the commercial pressures in a March 1997 article.

"Consumer protection advocates want to have drugs worked up well and thoroughly evaluated for safety and efficacy before getting on the market," Woodcock wrote in the Food and Drug Law Journal. "On the other hand, there are economic pressures to get drugs on the market as soon as possible, and these are highly valid."

But this summer--following the eighth and ninth drug withdrawals--Woodcock said the FDA cannot rely on labeling precautions, alone, to resolve safety concerns.

"As medical practice has changed . . . it's just much more difficult for [doctors] to manage" the expanded drug supply, Woodcock said in an interview. "They rely upon us much more to make sure the drugs are safe."

Another FDA administrator, Dr. Florence Houn, voiced similar concern in remarks six months ago to industry officials: "I think the lessons learned from the drug withdrawals make us leery."

Yet the imperative to move swiftly, cooperatively, remains.

"We are now making decisions more quickly and more predictably while maintaining the same high standards for product safety and efficacy," FDA Commissioner Jane E. Henney said in a National Press Club speech on Dec. 12.

Motivated by AIDS

The impetus for change at the FDA emerged in 1988, when AIDS activists paralyzed operations for a day at the agency's 18-story headquarters in Rockville, Md. They demanded immediate approval of experimental drugs that offered at

least a ray of hope to those otherwise facing death.

The FDA often was taking more than two years to review new drug applications. The pharmaceutical industry saw a chance to loosen the regulatory brakes and expedite an array of new products to market. The companies and their Capitol Hill lobbyists pressed for advantage: If unshackled, they said, the companies could invent and develop more remedies faster.

The political pressure mounted, and the FDA began to bow. By 1991, agency officials told Congress they were making significant progress in speeding the approval process.

The emboldened companies pushed for more. They proposed that drugs intended for either life-threatening or "serious" disorders receive a quicker review.

"The pharmaceutical companies came back and lobbied the agency and the Hill for that word, 'serious,' " recalled Jeffrey A. Nesbit, who in 1991 was chief of staff to FDA Commissioner David A. Kessler. "Their argument was, 'Well, OK, there's AIDS and cancer. But there are drugs [being developed] for Alzheimer's. And that's a serious illness.' They started naming other diseases. They began to push that envelope."

The wielding of this single, flexible adjective--"serious"--swung wide the regulatory door knocked ajar by the AIDS crisis.

New Order Takes Hold

In 1992, Kessler issued regulations giving the FDA discretion to "accelerate approval of certain new drugs" for serious or life-threatening conditions. That same year a Democrat-controlled Congress approved and President Bush signed the Prescription Drug User Fee Act. It established goals that call for the FDA to review drugs within six months or a year; the pharmaceutical companies pay a user fee to the FDA, now $309,647, with the filing of each new drug application.

The newly elected Clinton administration climbed aboard with its "reinventing government" project. Headed by Vice President Al Gore, the project called for the FDA, by January 2000, to reduce "by an average of one year the time required to bring important new drugs to the American public." As Clinton put it in a speech on March 16, 1995, the objective was to "get rid of yesterday's government."

For the FDA's medical reviewers--the physicians, pharmacologists, chemists and biostatisticians who scrutinize the safety and effectiveness of emerging drugs--a new order had taken hold.

The reviewers work out of public view in secure office buildings clustered along Maryland's Route 355. At the jet-black headquarters building, the decor is institutional, the corridors and third-floor cafeteria without windows. The reviewers examine truckloads of scientific documents. They are well-educated; some are highly motivated to do their best for a nation of patients who unknowingly count on their expertise.

One of these reviewers was Michael Elashoff, a biostatistician who arrived at the FDA in 1995 after earning degrees from UC Berkeley and the Harvard School of Public Health.

"From the first drug I reviewed, I really got the sense that I was doing something

worthwhile. I saw what a difference a single reviewer can make," said Elashoff, the son and grandson of statisticians.

Last year he was assigned to review Relenza, the new flu drug developed by Glaxo Wellcome. He recommended against approval.

"The drug has no proven efficacy for the treatment of influenza in the U.S. population, no proven effect on reducing person-to-person transmissibility, and no proven impact on preventing influenza," Elashoff wrote, adding that many patients would be exposed to risks "while deriving no benefit."

An agency advisory committee agreed and on Feb. 24 voted 13 to 4 against approving Relenza.

After the vote, senior FDA officials upbraided Elashoff. They stripped him of his review of another flu drug. They told him he would no longer make presentations to the advisory committee. And they approved Relenza as a safe and effective flu drug.

Lost Faith in the System

Elashoff and other FDA reviewers discern a powerful message.

"People are aware that turning something down is going to cause problems with [officials] higher up in FDA, maybe more problems than it's worth," he said. "Before I came to the FDA I guess I always assumed things were done properly. I've lost a lot of faith in taking a prescription medicine."

Elashoff left the FDA four months ago.

"Either you play games or you're going to be put off limits . . . a pariah," said Dr. John L. Gueriguian, a 19-year FDA medical officer who opposed the approval of Rezulin, the ill-fated diabetes drug. "The people in charge don't say, 'Should we approve this drug?' They say, 'Hey, how can we get this drug approved?'"

Said Dr. Rudolph M. Widmark, who retired in 1997 after 11 years as a medical officer: "If you raise concern about a drug, it triggers a whole internal process that is difficult and painful. You have to defend why you are holding up the drug to your bosses. . . . You cannot imagine how much pressure is put on the reviewers."

The pressure is such that when a union representative negotiated a new employment contract for the reviewers last year, one of his top priorities was to defend what he called the "scientific integrity" of their work.

"People feel swamped. People are pressured to go along with what the agency wants," said Dr. Robert S.K. Young, an FDA medical officer who in 1998 formed a union chapter to represent the reviewers. "You're paying for these highly educated, trained people, and they're not being allowed to do their job."

Each new drug application is accompanied by voluminous medical data, enough at times to fill 1,000 or more phone books. The reviewers must master this material in less than six months or a year, while juggling other tasks.

"The devil is in the details, and detail is something we no longer have the time to go into," said Gurston D. Turner, a veteran pharmacologist with the FDA's scientific investigations division who retired this year. "If you know you must

have your report done by a certain date, you get something done. That's what they [top FDA officials] count, that's all they count. And that is really, to me, a worrisome thing."

The FDA did spur reviewers to move at record speed.

In 1994, the FDA's goal was to finish 55% of its new drug reviews on time; the agency achieved 95%. In 1995, the goal was 70%; the FDA achieved 98%. In 1996, the goal was 80%; the FDA achieved 100%. In both 1997 and 1998, the goal was 90% and the FDA achieved 100%.

From 1993 to 1999 the agency approved 232 drugs regarded as "new molecular entities," compared with 163 during the previous seven years, a 42% increase.

The time-limit goals quickly were treated as deadlines within the FDA--imposing relentless pressure on reviewers and their bosses to quickly conclude their work and approve the drugs.

"The goals were to be taken seriously. I don't think anybody expected the agency to make them all," said William B. Schultz, a deputy FDA commissioner from 1995 to 1999.

Schultz, who helped craft the 1992 user-fee act as a congressional staff lawyer, added: "You can meet the goal by either approving the drug or denying the approval. But there are some who argue that what Congress really wanted was not just decisions, but approvals. That is what really gets dangerous."

Indeed, the FDA drug center's 1999 annual report referred to the review goals as "the law's deadlines." And, Dr. Woodcock, the center director, elaborated in a subsequent agency newsletter:

"In exchange [for the user fees], FDA makes a commitment to meet certain goals for review times. [The agency] has exceeded almost all of the goals, and it expects to continue to exceed them. Basically, the number of new approved drugs has doubled, and the review times have been cut in half."

The user fees have enabled the FDA to hire more medical reviewers. Last year, 236 medical officers examined new drugs compared with 162 officers on duty in 1992, the year before the user fees took effect.

Even so, Woodcock acknowledged in an FDA publication this fall that the workloads and tight performance goals "create a sweatshop environment that's causing high staffing turnover."

An FDA progress report in 1998, describing the work of agency chemists, said that "too many reviews are coming 'down to the wire' against the goal date. . . . This suggests a system in stress."

Said Nesbit, the former aide to Commissioner Kessler: "The clock is always running, whereas before the clock was never running. And that changes people's behavior."

Dozens of officials interviewed by The Times made similar observations.

"The pressure to meet deadlines is enormous," said Dr. Solomon Sobel, 65, director of the FDA's metabolic and endocrine drugs division throughout the 1990s. And the pressure is not merely to complete the reviews, he said. "The basic

message is to approve."

Over the last seven years, "there has been a huge shift," said Kathleen Holcombe, a former FDA legislative affairs staffer and congressional aide who now is a drug industry consultant. "FDA, historically, had an approach of, 'Regulate, be tough, enforce the law [and] don't let one thing go wrong,' " Holcombe said, adding that now, "the FDA sees itself much more in a cooperative role."

The perception of coziness with drug makers is perpetuated by potential conflicts of interest within the FDA's 18 advisory committees, the influential panels that recommend which drugs deserve approval or should remain on the market. The FDA allows some appointees to double as consultants or researchers for the same companies whose products they are evaluating on the public's behalf. Such was the case during committee appraisals of several of the recently withdrawn drugs, including Lotronex and Posicor, The Times found.

Few doubt the $100-billion pharmaceutical industry's clout. Over the last decade, the drug companies have steered $44 million in contributions to the major political parties and to candidates for the White House and both houses of Congress.

The FDA reviewers said they and their bosses fear that unless the new drugs are approved, companies will erupt and Congress will retaliate by refusing to renew the user fees. This would cripple FDA operations--and jeopardize jobs.

The companies' money now covers about 50% of the FDA's costs for reviewing proposed drugs--and agency officials say that persuading Congress to renew the user fees into 2007 is now a top priority.

Yet even if the user fees remain, the FDA is prohibited from spending the revenue for anything other than reviewing new drugs. So while the budget for pre-approval reviews has soared, the agency has gotten no similar increase of resources to evaluate the safety of the drugs after they are prescribed.

"It's shocking," said Dr. Brian L. Strom, chairman of epidemiology at the University of Pennsylvania. "How can you say, 'Release drugs to the market sooner,' and not know if they're killing people? . . . It really is a dramatic statement of public priorities."

More than 250,000 side effects linked to prescription drugs, including injuries and deaths, are reported each year. And those "adverse-event" reports by doctors and others are only filed voluntarily. Experts, including Strom, believe the reports represent as few as 1% to 10% of all such events.

"There's no incentive at all for a physician to report [an adverse drug reaction]," said Strom, who has documented the phenomenon. "The underreporting is vast."

Even when deaths are reported, records and interviews show that companies consistently dispute that their product has caused a given death by pointing to other factors, including preexisting disease or use of another medicine.

To be sure, a chain of events affects the safe use of a prescription drug: The companies' conduct of clinical studies; the FDA's regulatory actions; the doctor's decision to prescribe; the pharmacist's filling of a handwritten prescription; the patient's ability to take the drug as directed. A lapse at any link could prove fatal.

And once a pill is approved by the FDA, the manufacturer often spends heavily on promotion to seize the largest possible market share. This can exacerbate the risk to public health, according to experts.

"Aggressive promotion increases exposure--and doesn't give you the time to find the problem before patients get hurt," said Dr. Raymond L. Woosley, pharmacology department chairman at Georgetown University and a former FDA advisory committee member.

When serious side effects emerge, the FDA officials have championed using package labeling as a way to, in their words, "manage" risks. Yet the agency typically has no way to know if the labeling precautions--dense, lengthy and in tiny print--are read or followed by doctors and their patients.

The FDA often addresses unresolved safety questions by asking companies to conduct studies after the product is approved. But the research frequently is not performed--prompting the inspector general of the Department of Health and Human Services to say in 1996 that "FDA can move to withdraw drugs from the market if the post-marketing studies are not completed with due diligence."

Since that report was issued, the FDA has not withdrawn any drug due to a company's failure to complete a post-approval safety study. Officials conceded this week that they still do not know how often the studies are performed.

One consequence is that greater risk is shifted to doctors and patients.

For example, Woodcock and her senior aides allowed Rezulin to remain on the U.S. market nearly 2½ years after it was withdrawn in Britain in December 1997. The FDA recommended frequent laboratory testing of patients using the drug but had no scientific assurance that the tests would prevent Rezulin-induced liver failure.

"They kept increasing the number of liver-function tests you should have," noted Dr. Alastair J.J. Wood, a former FDA advisory committee member who is a professor of medicine at Vanderbilt University. "That was clearly designed to protect the FDA, to protect the manufacturer, and to dump the responsibility on the patient and the physician. If the patient developed liver disease and he hadn't had his [tests] done, somebody was to blame and it wasn't the manufacturer and it wasn't the FDA."

Industry Assurances

Leading industry officials say Americans have nothing to fear from the wave of drug approvals.

"Do unsafe drugs enter and remain in the marketplace? Absolutely not," said Dr. Bert A. Spilker, senior vice president for scientific and regulatory affairs for the Pharmaceutical Research and Manufacturers of America, in remarks last year to industry and FDA scientists.

But during interviews over the last two years, current and former FDA specialists cited repeated instances when drugs were approved with less than compelling evidence of safety or effectiveness. They also said that important information has been excluded from the labels on some medications.

Elashoff, for instance, was surprised at the labeling for a drug called Prograf,

approved in 1997 to prevent rejection of transplanted kidneys. The drug first had been approved in 1994 for use among liver-transplant patients.

The new label notes that Prograf was proved effective in a study of 412 U.S. kidney transplant patients. But no mention is made of the company's 448-patient European study, in which 7% of the patients who took Prograf died--double the 3.5% death rate among those who received a different anti-rejection drug, documents show.

An auditor from the FDA's scientific investigations unit, Antoine El-Hage, examined the European study results and concluded the "data are reliable." Elashoff agreed in his review.

Yet the only way for doctors or patients to find that data is to search the medical literature or seek the FDA's review documents.

Excluding the European study from the Prograf label, Elashoff said, "was just a total whitewash. . . . I think any rational person would reconsider taking this drug if they knew what happened in Europe."

A spokesman for the manufacturer of Prograf said the company had no objection to including the European study results in the labeling. William E. Fitzsimmons, a vice president of drug development for Fujisawa Healthcare Inc., said the decision to exclude the results was entirely the FDA's.

"We submitted that data," he said. "It came down to what the FDA was comfortable putting in the label. . . . We certainly have no interest in trying to hide that information. We presented it at major meetings on transplantation. . . . We're comfortable with that information being out in the public domain."

But if the FDA had included the European results in the label, it would have impugned the agency's basis for approving the new, expanded use for Prograf, according to Elashoff and others.

Asked why the agency excluded the information, Woodcock said the European results were "unreliable . . . and could be potentially misleading to doctors and patients in the U.S. if these were included in the label."