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At F.D.A., Strong Drug Ties and Less Monitoring

Gardiner Harris, John Schwartz contributed reporting for this article.. **New York Times**. (Late Edition (East Coast)). New York, N.Y.: Dec 6, 2004. pg. A.1

Abstract (Summary)

At the time, Seldane was the fifth-most popular drug in the nation, and the antifungal medicine was common, too. Such a serious interaction between two popular drugs was worrisome. Dr. [Lou Cantilena] reported the problem to the F.D.A. and Seldane's maker, now known as Sanofi-Aventis. The F.D.A. cannot require drug makers to test already-approved medicines. Instead, it can urge companies to do more testing, can change warning labels or, as a last resort, can take the product off the market.

Sam Kazman, general counsel of the Competitive Enterprise Institute, a libertarian group in Washington, said that is how it should be. Mr. Kazman has been fighting for years against F.D.A. regulations, which he said had kept important medicines away from patients. Doctors and patients should decide what drugs are right for them, not the F.D.A., Mr. Kazman said. "Giving them more money is no reason to think they would improve and it's possible that just the opposite would happen," he said.

Dr. [David A. Kessler], former Food and Drug Administration chief. (Photo by John Duricka/Associated Press); Dr. [David J. Graham], a reviewer in the F.D.A. office of drug safety, was critical of the agency in an appearance before a Congressional panel last month. Dr. Graham has blamed agency policies for the delay in uncovering the dangers of the arthritis drug Vioxx. (Photo by Daniel Hulshizer/Associated Press); (Photo by Chris Kleponis/Bloomberg News); Protesters in Manhattan in 1988 criticized the federal government's response to AIDS, claiming that it was delaying treatments. (Photo by Chester Higgins Jr./The New York Times)(pg. A20)

Full Text (3712 words)

When federal drug officials suspected in 1992 that a popular allergy pill might cause heart problems, they turned to their own scientists. Their trial confirmed the danger, and the drug was pulled from the market.

Eight years later, similar worries surrounded the arthritis pill Vioxx. But by then, the Food and Drug Administration had shifted gears, slashing its laboratories and network of independent drug safety experts in favor of hiring more people to approve drugs, changes that arose under an unusual agreement that has left the agency increasingly reliant on and bound by drug company money. Discovering Vioxx's dangers would take four more years.

That delay has led to a firestorm of criticism. Members of Congress, an internal F.D.A. whistleblower and prominent medical journals have said the agency is incapable of uncovering the perils of drugs that have been approved and are in wide distribution. Some have accused it of being cozy with drug makers.

Dozens of former and current F.D.A. officials, outside scientists and advocates for patients say the agency's efforts to monitor the ill effects of drugs that are on the market are a shadow of what they should be because the White House and Congress forced a marriage between the agency and industry years ago for the rich dowry that industry offered.

Under the 1992 agreement, the industry promised to give the agency millions -- in the 2003 fiscal year, $200 million -- but only if the agency spent a specified level of money on new drug approvals.

As Congressional support sank since then, the agency has cut everything else but new drug reviews. In the past 11

years, spending on the reviews has increased to more than four-fifths of the budget of the agency's drug center from about half.

Among the priorities that took the worst hit was ensuring the safety of the drugs that patients are already taking. Drug companies test their products in people before they are approved, but sometimes potentially serious problems arise only when they are being used by millions of people. The F.D.A. has never been able to require drug makers to undertake new safety tests once a drug is approved, so tracking the safety of drugs already on the market is the agency's responsibility.

But as a result of the agency's shifting its resources, almost everyone, including critics, outside drug safety experts, medical journal editors, some industry executives and even top agency officials, now agrees that its mechanisms for uncovering the dangers of drugs after they have been approved are woefully inadequate, particularly, as was the case of Vioxx, when the potentially damaging side effect is not an unusual ailment.

The F.D.A.'s present safety monitoring system "is not good for determining if a drug increases the rate of a side effect already common in the population," said Dr. Janet Woodcock, acting deputy commissioner for operations at the agency.

Indeed, the agency now relies almost entirely on the willingness of drug makers to report problems that crop up after a drug has been approved to ensure the safety of the nation's drug supply. Some critics say this dependency has gradually worn away at the agency's willingness to confront drug makers, making it timid and leaving patients vulnerable.

"This is not just about dollars," said Dr. Jerry Avorn, a professor at Harvard Medical School and the author of "Powerful Medicines." "It's a cultural issue in which the agency feels it can't pressure drug makers."

Now lawmakers are considering proposals for a center for drug safety that would be independent of the agency's new drug reviewers. The departing health and human services secretary, Tommy G. Thompson, said Friday that he favored creating such a center. After initially opposing the idea, agency officials have said they will study any proposals.

These proposals may not have been needed if not for the details of the 1992 agreement, which began with the best of intentions. AIDS, cancer, heart disease -- all were terrible diseases that drug makers' laboratories were confronting. But their remedies were languishing for years on F.D.A. shelves because the agency did not have the money to hire enough reviewers.

The drug industry agreed to chip in. Indeed, half of the budget for the agency's Center for Drug Evaluation and Research, the principal office that oversees drug reviews and safety, will come from drug industry user fees, up from nothing in 1992 and 31 percent in 1998. But these millions come with strings.

More Money for Reviews

The 1992 agreement provided that the F.D.A. could collect fees from industry only if government financing of new drug reviews, adjusted for inflation, never fell below 1992 levels (later revised to 1997 levels). This stipulation was intended by industry to ensure that its money was used to hire new drug reviewers and not simply substitute for government support of those already on staff.

But Congressional financing has lagged the agency's escalating payroll costs. To meet the "trigger" and keep fees flowing, agency officials have been forced to shift dollars from other programs into new drug reviews. This shifting has increased the agency's focus on the reviews even beyond what the drug industry had negotiated.

In 1992, the agency's drug center spent 53 percent of its budget on new drug reviews. The rest went to survey programs, laboratories and other efforts that in part helped ensure that drugs already on the market were safe. In 2003, 79 percent of the agency's drug center budget went to new drug reviews. Everything else has gotten squeezed.

"We get increased user funds and not increased appropriated dollars," said Deborah Henderson, director of the office of executive programs in the F.D.A.'s drug center. "We have stolen from the labs and other parts of the non-user fee program."

Since the 1992 agreement, agency officials have eliminated half of the scientists in the drug center's laboratories and starved them of new equipment. They have ended many of the agency's collaborations with academic groups that scrutinize the problems of marketed drugs. To pay for a modest in-house effort to catalog some information on drug side effects, a system called the Adverse Event Reporting System, the agency has raided furniture and travel

budgets.

Dr. Woodcock said she shut down laboratories and many outside grant programs to try and raise the money to keep the agency's side effect reporting system.

The industry's influence even extends to perks given agency employees. Under the 1992 agreement, which was renewed in 1997 and 2002, new drug reviewers have travel and training budgets that allow them to attend far-flung conferences and courses. Those who work in the agency's office of drug safety get two-thirds less, which keeps most at home.

The agreement that accepted such a large proportion of industry financing "made a bad situation worse," Dr. David J. Graham, a reviewer in the agency's office of drug safety who harshly criticized the agency before a Congressional panel last month, said in an interview. "The agency was already far too focused on approvals and not on safety."

"And if this problem isn't fixed," Dr. Graham said, "future Vioxx-like catastrophes are inevitable."

Dr. David A. Kessler, former commissioner of the agency and now dean of the University of California San Francisco Medical School, said the financing agreements with industry "increasingly micromanage the F.D.A."

"They reinforce the focus on new drug review over the agency's field and post-marketing surveillance efforts," Dr. Kessler said.

Sammie Young, a drug safety inspector for the agency from 1963 until 1992, said that by the time he left the agency had become wholly focused on drug approvals -- to the delight of industry. Those at the agency "decided their main goal in life was to approve drugs," Mr. Young said.

The decline in the agency's commitments to monitor the safety of approved medicines started in the Clinton administration and continues today. Most experts who track drug side effects say the remedy is more money, perhaps provided by a tax on prescriptions. But others complain that the agency spends far too much already, and some agency critics contend that, more than dollars, what it really needs is more courage to confront drug makers about safety problems.

While its $1.8 billion budget and staff of 10,800 are small by federal government standards, the Food and Drug Administration is among the most important bodies of the federal government. It is the principal overseer for the pharmaceutical, food, medical device and animal feeds industries. Its rules affect nearly 100,000 businesses producing more than $1 trillion worth of goods a year, or about a quarter of the American economy.

Founded in 1906, the agency was at first charged simply with ensuring that claims made on medicine packages were not demonstrably false. But scandal after scandal in the intervening decades led to legislation expanding its powers.

In 1984 a law established a generic drug industry that could capture sales from drug makers once patents on medicines expired. The law led brand-name drug makers to push for quicker review times to maximize sales during the patented period.

And then came AIDS.

As the disease swept through gay communities in San Francisco and New York, people desperate for remedies scoured the world. When AZT showed promise in early trials, the F.D.A. allowed the drug to be distributed to patients before its formal approval.

In 1988, AIDS protesters besieged the agency's offices, raising a black flag on its flag pole and contending that it was actively delaying treatments. The agency responded by allowing potentially life-saving drugs to be widely distributed while undergoing review. Still, it was not enough. Advocates for cancer patients complained about long review times as well. With Congress feeling tightfisted, almost all agreed that the agency needed more money and that the drug industry was the best source to tap. A result was the 1992 agreement. The industry agreed to underwrite the hiring of new drug reviewers if the agency would agree to tight review timelines. Peter Barton Hutt, a former general counsel for the agency, helped negotiate the agreement on behalf of drug makers.

"Clearly the industry forced F.D.A. to pay attention to the industry's agenda, and that has always been to shorten the drug approval process," Mr. Hutt said.

Some who supported the agreement then regret it now. Dr. Sidney Wolfe, director of Public Citizen's health research group, said it had pushed the agency into the drug industry's arms and led to poorer drug reviews.

But William B. Schultz, who worked at Public Citizen and then in Congress and was deputy commissioner for policy at the F.D.A. from 1994 to 1998, said the agreement saved the agency. In 1996, Republicans lawmakers led by Newt Gingrich, the house speaker, proposed legislation that would have allowed companies to market their products without agency review, gutting its oversight authority.

Proof that the agency had halved its drug review times since the 1992 agreement passed undermined the proposals, Mr. Schultz said. "Their argument was the drug lag, but it fell apart because by then the lag had been eliminated," he said.

A Question of Care

Almost every argument about the 1992 agreement revolves around review times and whether new drug reviews are as careful as in the past. Many outside the agency say the rapid review timelines adopted as part of the agreement have made the agency's drug reviews sloppy, leading the agency to approve drugs like Vioxx that should never have gotten onto the market. Merck withdrew Vioxx in September after a test showed that it doubled the risk of heart attacks.

Top agency officials fiercely disagree with this criticism, pointing out that the ratio of drugs withdrawn compared with those approved has held steady for decades. Some dangerous side effects, they say, will never reveal themselves until millions use a medicine.

Drug industry officials also say this criticism is wrong. New drug reviews are at least as rigorous as they were a decade ago, they say.

Jeff Trewhitt, a spokesman for the drug industry's trade group, the Pharmaceutical Research and Manufacturers of America, said the fees paid by industry to the agency "do not pay for approval. They merely guarantee review of a product application by the F.D.A. in a set period of time."

Beyond new drug reviews, what is rarely discussed is the 1992 agreement's effect on post-approval monitoring of drug side effects. Independent scientists had long helped the agency not only flag possible problems, but also through tests confirm them. Some gave patients drugs and measured the effects. Others combed through millions of patient records at giant managed-care companies to spot problems among those given certain medicines.

Dr. Susan Jick, co-director of the Boston Collaborative Drug Surveillance Program, one of the nation's largest and longest-running initiatives to uncover drug side effects, said F.D.A. officials told her that the agency was ending its support after 20 years because her program was using British data. Dr. Brian Strom at the University of Pennsylvania, who worked with the agency on drug side effect issues for decades until recently, was told that there was no money. Others were told the same thing.

None knew that the reason was that money had to be shifted out of their programs into new drug reviews to satisfy the requirements of the agreement and industry demands.

Dr. Lou Cantilena, head of the division of clinical pharmacology and medical toxicology at the Uniformed Services University of the Health Science in Bethesda, Md., not only helped the agency study drug safety issues for years but also trained its staff. Both programs were ended in the late 1990's.

Dr. Cantilena said the agency was now almost wholly reliant on the drug industry for tests of side effects. He said he was more aware than most about the dangers of this situation.

In December 1989, a woman walked into Bethesda Naval Hospital complaining that she kept passing out. Doctors placed her on a heart monitor, and it showed a frightening heart arrhythmia. Dr. Cantilena and his team of drug experts were called in. The woman was taking Seldane for allergies. An overdose of Seldane was known to cause heart arrhythmias, but the woman insisted that she had taken only a pill a day.

The doctors were stumped until the woman revealed that she had also been taking an antifungal drug to treat a vaginal yeast infection. The antifungal was known to interfere with the breakdown of other drugs. Blood tests showed high levels of Seldane. Dr. Cantilena concluded that the woman had suffered from a drug-to-drug interaction.

At the time, Seldane was the fifth-most popular drug in the nation, and the antifungal medicine was common, too. Such a serious interaction between two popular drugs was worrisome. Dr. Cantilena reported the problem to the F.D.A. and Seldane's maker, now known as Sanofi-Aventis. The F.D.A. cannot require drug makers to test already-approved medicines. Instead, it can urge companies to do more testing, can change warning labels or, as a last resort, can take the product off the market.

So the agency asked Dr. Cantilena to perform the study. He recruited six healthy volunteers, hooked them up to heart monitors and gave them Seldane and the antifungal. Four of the volunteers developed heart arrhythmias so severe that Dr. Cantilena ended the study early.

Within weeks of reporting his results to the F.D.A., the agency announced that it was placing a severe warning on Seldane's label about the interaction. In 1997, the maker withdrew Seldane from the market because of the problem.

The agency has almost no ability to perform similar tests now, Dr. Cantilena said.

Tracking Safety

Perhaps even more pressing, the agency has no continuing ability to uncover the kind of life-threatening drug side effects that sidelined Vioxx.

Presently, the main drug program to catalog the dangers of drugs is a computer listing of side-effects. It is a passive system, meaning that doctors report side effects only when they think of it and have the time. The system receives almost 400,000 reports a year, but these represent a small fraction of the total, all agree. Most reports are delivered by drug makers, who hear about side effects from physicians.

The side effects tracking system can signal problems only when a drug causes an effect like liver failure that is normally very rare. If a drug increases the number of heart attacks, a problem that is very common normally, the system is useless, Dr. Woodcock of the F.D.A. said.

Realizing this weakness, Dr. Graham of the agency's office of drug safety collaborated with Kaiser Permanente, a huge health maintenance organization, to check its computer records to see if those taking Vioxx had had more heart attacks. The study took nearly four years to complete. Its results became known in August and demonstrated Vioxx's dangers.

Dr. David Campen, medical director of Kaiser's pharmacy operations, said the study would have taken half the time if the agency had had the money to pay for drug monitoring programs with Kaiser or other large managed care organizations. Dr. Graham has estimated that the delay in uncovering Vioxx's dangers cost 55,000 Americans their lives, a number top officials at the F.D.A. have labeled as "junk science."

An adequate system for monitoring side effects may have prevented some of the deaths.

Dr. Strom of the University of Pennsylvania said the F.D.A.'s almost complete focus on approving new drugs at the expense of ensuring the safety of medicines that patients are already taking is wrong.

"They're getting all these drugs on the market a whole lot sooner and not looking at what happens once they get there," he said.

Seeking Improvements

Some top agency officials are keenly aware of these problems. In 1999, an agency task force wrote a 106-page report cataloging the agency's weaknesses and calling for reforms. "F.D.A. is not funded, staffed or in some cases authorized to collect" comprehensive reports of problems with drugs once they are already being sold, the report concluded.

In a March 13, 2000, letter to Senator Jim Jeffords, an independent from Vermont, Dr. Woodcock wrote that more than 1.6 million people in the United States were hospitalized every year because of drug side effects. Half of these problems are preventable, she wrote. The agency needed more money for better systems to prevent these problems, she wrote. The agency did not get them.

Sam Kazman, general counsel of the Competitive Enterprise Institute, a libertarian group in Washington, said that is how it should be. Mr. Kazman has been fighting for years against F.D.A. regulations, which he said had kept important medicines away from patients. Doctors and patients should decide what drugs are right for them, not the F.D.A., Mr. Kazman said. "Giving them more money is no reason to think they would improve and it's possible that just the opposite would happen," he said.

And Dr. Avorn of Harvard Medical School said that what the agency needed more than money was courage. When doubts emerge about a medicine's safety, the agency needs to insist that drug makers pay for independent tests, he said. And continuing drug surveillance could also be paid for by drug makers, he said.

If companies refuse, the agency "needs to call a press conference and issue a public notice saying, 'There are unresolved issues and we are trying to get the company to do a clinical trial and doctors should take that into

account,'" Dr. Avorn said. "The F.D.A. has moral authority and extraordinary public relations power if they chose to use them."

The agency has asked the Institute of Medicine, the government's principal scientific review agency, to study the agency's system for monitoring the safety of marketed drugs. Pressure for an independent drug safety center grew on Friday when Mr. Thompson of health and human services said in a news conference to announce his resignation that he supported such a move.

The reason to make decisions governing the safety of drugs already on the market independent of the groups that approve new drugs, Dr. Graham of the F.D.A. told a Senate panel last month, is the conflicts that inevitably arise when those who approve a drug must later decide whether their own decisions were mistaken.

"They approved the drug so there can't possibly be anything wrong with it," Dr. Graham told the panel.

But many inside the F.D.A. say that separating the monitoring of side effects from drug approvals would be a mistake because a drug's risks cannot be assessed independently from its benefits. Besides, information about the safety of drugs already approved should be used to assess applications for experimental drugs in the same class, said Dr. David Feigal, a top agency official who retired in May. An independent drug safety center "is exactly the wrong way to go," Dr. Feigal said.

Agency officials initially opposed making an independent drug safety center but have recently said they would study any proposals. Some have privately said that if Congress agrees to give such an independent center substantial resources the change could be worth the extra money.

[Photograph]
Dr. David A. Kessler, former Food and Drug Administration chief. (Photo by John Duricka/Associated Press); Dr. David J. Graham, a reviewer in the F.D.A. office of drug safety, was critical of the agency in an appearance before a Congressional panel last month. Dr. Graham has blamed agency policies for the delay in uncovering the dangers of the arthritis drug Vioxx. (Photo by Daniel Hulshizer/Associated Press); (Photo by Chris Kleponis/Bloomberg News); Protesters in Manhattan in 1988 criticized the federal government's response to AIDS, claiming that it was delaying treatments. (Photo by Chester Higgins Jr./The New York Times)(pg. A20)

[Chart]
"Influencing Priorities"
A 1992 arrangement between the Food and Drug Administration and drug companies led to a dependence on corporate money to finance much of its drug testing efforts.
A GROWING SHARE of the budget for the F.D.A.'s Center for Drug Evaluation and Research goes to new drug approvals, with a smaller share for drug safety.
Graph tracks percent of the F.D.A's budget is used for Drug Evaluation and Research and what percent is used for Drug safety since 1993.
INDUSTRY USER FEES collected by the F.D.A. to finance its work have ballooned.
Graph tracks amount of Industry User Fees were collected by the F.D.A. to finance its work since 1993.
In 2003 dollars
(Source by Food and Drug Administration)(pg. A20)

Indexing (document details)

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