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DANGEROUS PRESCRIPTION
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David Archer had high cholesterol but was otherwise in good health in the fall of 2000 when he began taking Baycol, a cholesterol-lowering "statin" drug that the Food and Drug Administration (FDA) had recently approved to be sold at a dosage four times higher than the originally approved dose. About two months after starting the higher-dosage drug, Archer would be dead.

What David Archer hadn't known was that more than five months before his death, the drug's manufacturer, Bayer, had received strong indications that Baycol might be many times more likely than other statin drugs to cause a rare, life-threatening muscle wasting side effect known as Rhabdomyolisis. Following Archer's death, it would be another eight months before Bayer would voluntarily remove the drug from the market in August 2001 because of this side effect.

"David was always very active—he would chop trees, he would do a lot of things," his wife, Lucy Archer recalls. "…He should have never, never died."

David Archer is not alone. He is just one of the tens of thousands of Americans who have become ill or died after taking medications approved by the FDA. For many consumers, FDA approval signifies that a drug or product has been found to be safe. But just how much does the average American know about the FDA approval process and what it can—and cannot—do? How good is the FDA's system for identifying drugs that cause harm? And what happens when a harmful product makes its way into consumers' hands?

In "Dangerous Prescription," airing Thursday, November 13, at 9 P.M. on PBS (check local listings), FRONTLINE® investigates the integrity of America's drug safety system. Through interviews with current and former FDA officials, pharmaceutical industry representatives, and consumers, the one-hour documentary examines the FDA's handling of several approved drugs that were later pulled from the market after causing injuries and even deaths. The program also examines the role that drug companies play in the approval and monitoring of prescription drugs and questions whether the FDA's current system is adequate for protecting the public safety.

"I think Americans need to recognize that every time they put a pill in their mouth—especially a new pill that they've never taken before—it's an experiment," says Dr. Raymond Woosley, dean of the University of Arizona College of Medicine.

Since 1997, more than a dozen drugs have been taken off the market due to severe side effects or injuries. It's a statistic that may surprise the many U.S. consumers who believe that FDA approval guarantees a drug's safety.

Not so, say scientists and industry observers.

"When a drug goes on the market, only about 3,000 patients have ever been given that drug," says Woosley, who directs a national center that studies drug side effects. "We will never know all the toxicity that can occur, especially the one [patient] in 10,000 or one in 20,000 that could be seriously harmed. Our detection will only happen after the drug is on the market and exposed to a huge number of patients."

At that point, agency officials say, the FDA depends almost completely on a system that relies on individual doctors and clinicians throughout the country to spot serious side effects or injuries and voluntarily report them to the FDA's Office of Drug Safety.

"In the United States, the initiator of the report does so on a voluntary basis," confirms Paul Seligman, director of the FDA's Office of Drug Safety. "It's critical that we get these reports. There's no other way the FDA has for understanding what's going on with a medicine once it's been marketed."

In most cases, doctors will report side effects not to the FDA but to the drug's manufacturer; when this happens, the company is required by law to report the information to the FDA within fifteen days of receiving it. This is the FDA's "Medwatch" system, but some observers and industry insiders see a flaw in it.

"The FDA is wholly dependent on trust—trusting that the company is providing all the truth, all the time," retired FDA drug reviewer Dr. Leo Lutwak says. "And that the company is not hiding information. And that the company is not covering up information."

In "Dangerous Prescription," FRONTLINE recounts how Bayer delayed notifying the FDA of the suspected link between its cholesterol-lowering Baycol drug and a higher risk of Rhabdomyolisis while it conducted studies to see if the suspicions could be confirmed. At the same time, Bayer continued to sell and aggressively promote Baycol, which cost 30 percent less than its main competitor, Lipitor.

"What the drug company chose to do was study it further, and continue marketing the drug as aggressively as possible," says Kip Petroff, an attorney representing consumers injured by Baycol.

When the FDA approved the release of the higher-dosage Baycol—known as Baycol .8—in the summer of 2000, the agency was unaware that Bayer had information suggesting that patients on Baycol had a significantly higher risk of developing Rhabdomyolisis than patients on other statin drugs. Bayer declined to be interviewed by FRONTLINE.

FRONTLINE also recounts the biggest safety disaster in the FDA's history: the approval and removal of the diet drugs known as Fen Phen and Redux. Fen Phen was a combination of Fenfluramine (also sold under the brand name Pondimin) and Phentermine. Redux was a slightly modified version of Fenfluramine called Dex-Fenfluramine. In "Dangerous Prescription," FRONTLINE speaks with scientists and former FDA officials who say the agency had evidence of the dangers of Redux before the drug was released but chose to approve it anyway.

Dr. Stuart Rich, a cardiologist at the Rush Heart Institute in Chicago, recalls that the FDA decision over whether to approve Redux for U.S. distribution occurred around the same time that he and his colleagues in France were wrapping up a three-year, European study of the drug. The study showed a strong correlation between pulmonary hypertension and diet drugs—particularly Redux.

"What was particularly shocking to me was that on the heels of reporting that this drug caused a fatal, incurable disease in Europe, that the company was planning to put it on the American marketplace," Rich tells FRONTLINE. "When I had heard this, I'd said, 'Well, you can try, but it's never gonna get in this country. The FDA would never permit a drug that had little benefit [and] terrible risk on the American marketplace.'"

Dr. Lutwak, then still employed at the FDA as a drug reviewer, agreed. "I thought it was an open and shut case," he says. "This was a dangerous group of drugs with very little, if any, benefit."

FRONTLINE recounts the internal review process that led the FDA to approve Redux over the concerns and objections of its own drug reviewers. Although Lutwak eventually agreed to the approval of Redux—with a number of restrictions—he was quite worried.

"I became concerned about the system," he says. "…And I was particularly concerned about the potential effect on thousands and millions of people who would be using the drug."

In "Dangerous Prescription," viewers meet North Dakota cardiologist Dr. Jack Crary, one of the first doctors to report a connection between Fen Phen and Redux and a different serious side effect—heart valve problems. Crary recalls wondering in the spring of 1997 why the FDA was failing to act on the many reports he had sent to Redux's manufacturer, Wyeth, about the heart

valve issue. "It was frustrating," Crary says. "I was frustrated enough that I called the FDA in May [1997], and the person I talked to at the FDA knew nothing about it."

It wasn't until Crary and his colleagues held a press conference in late June 1997 to announce their findings that the FDA would kick into high gear; within weeks, Redux and Pondimin were taken off the market—some six months after Crary first notified Wyeth of the problem.

More than 200,000 Americans either have sued or are planning to sue Wyeth in connection with Fen Phen. To date, the cases have cost Wyeth nearly $13 billion; ultimately, the cost to the company could be much higher. Wyeth declined to be interviewed by FRONTLINE.

The documentary also examines the impact of the Prescription Drug Users Fee Act—legislation passed by Congress that allows drug companies to pay a fee of more than $500,000 with each drug application so that the FDA can hire more drug reviewers—thereby speeding up the drug approval process. Critics say the law has pushed the FDA too close to the pharmaceutical companies it is charged with regulating. FRONTLINE speaks with a former FDA safety officer who recounts being pressured to tone down or alter negative drug reviews in order to speed approval of a new drug. Another tells of suffering agency retribution and retaliation for recommending against a drug's approval.

"This system has created a very unhealthy relationship between the industry and the FDA, where the FDA says, 'We have to be nice to these people because they are paying our bills,'" says Sidney Wolfe of the Public Citizens Health Research Group. "The culture at the FDA has become 'please the industry, avoid conflict, look upon our role as getting as many drugs approved as possible.'"

It's a charge FDA officials strongly deny. "We don't really feel pressure to please the industry…we just reject absolutely that we're influenced by that," says Steven Galson, deputy director of the FDA's drug division. But admits Galson, "Our system isn't perfect….I think the lesson is, there's a lot of room for us to go in terms of making improvements with the system."

Galson's words are of little comfort to people like Marlee Stewart, one of the North Dakota patients whose Fen Phen-related heart valve problems led to the weight loss drugs being removed from the market. Stewart will likely need surgery to replace her leaky heart valve.

"I am mad, angry, frustrated for the fact that they took a good part of my life away," she says. "They may have taken a good section of my life away. And I do understand that [drug companies] are in the business to make money, but I'm in the business to live."

"Dangerous Prescription" is a FRONTLINE co-production with Resolute Films, Inc. The writer, producer and director is Andy Liebman.

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