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When drug makers' profits outweigh penalties

By David Evans
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Prosecutor Michael Loucks remembers clearly when attorneys for Pfizer, the world's largest drug company, looked across the table and promised it wouldn't break the law again. ¶ It was January 2004, and the lawyers were negotiating in a conference room on the ninth floor of the federal courthouse in Boston, where Loucks was head of the health-care fraud unit of the U.S. Attorney's Office. One of Pfizer's units had been pushing doctors to prescribe an epilepsy drug called Neurontin for uses the Food and Drug Administration had never approved. ¶ In the agreement the lawyers eventually hammered out, the Pfizer unit, Warner-Lambert, pleaded guilty to two felony counts of marketing a drug for unapproved uses. New York-based Pfizer agreed to pay \$430 million in criminal fines and civil penalties, and the company's lawyers assured Loucks and three other prosecutors that Pfizer and its units would stop promoting drugs for unauthorized purposes. ¶ What Loucks, who was acting U.S. attorney in Boston until November, didn't know until years later was that Pfizer managers were breaking that pledge not to practice off-label marketing even before the ink was dry on their plea.

On the morning of Sept. 2, 2009, another Pfizer unit, Pharmacia & Upjohn, agreed to plead guilty to the same crime. This time, Pfizer executives had been instructing more than 100 salespeople to promote Bextra -- a drug approved only for the relief of arthritis and menstrual discomfort -- for treatment of acute pain of all kinds.

For this new felony, Pfizer paid the largest criminal fine in U.S. history: \$1.19 billion. On the same day, it paid \$1 billion to settle civil cases involving the off-label promotion of Bextra and three other drugs with the United States and 49 states.

"At the very same time Pfizer was in our office negotiating and resolving the allegations of criminal conduct in 2004, Pfizer was itself in its other operations violating those very same laws," Loucks, 54, says. "They've repeatedly marketed drugs for things they knew they couldn't demonstrate efficacy for. That's clearly criminal."

The penalties Pfizer paid for promoting Bextra off-label were the latest chapter in the drug's benighted history. The FDA found Bextra to be so dangerous that Pfizer took it off the market for all uses in 2005.

Across the United States, pharmaceutical companies have pleaded guilty to criminal charges or paid penalties in civil cases when the Justice Department finds that they deceptively marketed drugs for unapproved uses, putting millions of people at risk of chest infections, heart attacks, suicidal impulses or death.

It used to be legal for companies to promote drugs in the United States for any use. Congress banned the practice in 1962, requiring pharmaceutical companies to first prove their drugs were safe and effective for specific uses.

If the law is clear, why do drug companies keep breaking it? The answer lies in economics. Pharmaceutical companies spend about \$1 billion to develop and test a new drug. To recoup their investment, the companies want doctors to prescribe their drugs as widely as possible.

Since May 2004, Pfizer, Eli Lilly, [Bristol-Myers Squibb](#) and four other drug companies have paid a total of \$7

billion in fines and penalties. Six of the companies admitted in court that they marketed medicines for unapproved uses. In September 2007, New York-based Bristol-Myers paid \$515 million -- without admitting or denying wrongdoing -- to federal and state governments in a civil lawsuit brought by the Justice Department. The six other companies pleaded guilty in criminal cases.

In January 2009, Indianapolis-based Lilly, the largest U.S. psychiatric drugmaker, pleaded guilty and paid \$1.42 billion in fines and penalties to settle charges that it had for at least four years illegally marketed Zyprexa, a drug approved for the treatment of schizophrenia, as a remedy for dementia in elderly patients.

In five company-sponsored clinical trials, 31 people out of 1,184 participants died after taking the drug for dementia -- twice the death rate for those taking a placebo, according to an article in the Journal of the American Medical Association.

"Marketing departments of many drug companies don't respect any boundaries of professionalism or the law," says Jerry Avorn, a professor at Harvard Medical School. "The Pfizer and Lilly cases involved the illegal promotion of drugs that have been shown to cause substantial harm and death to patients."

The widespread off-label promotion of drugs is yet another manifestation of a health-care system that has become dysfunctional.

"It's an unbearable cost to a system that's going broke," Avorn says. "We can't even afford to pay for effective, safe therapies."

About 15 percent of all U.S. drug sales are for unapproved uses without adequate evidence the medicines work, according to a study by Randall Stafford, a medical professor at Stanford University.

As large as the penalties are for drug companies caught breaking the off-label law, the fines are tiny compared with the firms' annual revenue.

The \$2.3 billion in fines and penalties Pfizer paid for marketing Bextra and three other drugs cited in the Sept. 2 plea agreement for off-label uses amount to just 14 percent of its \$16.8 billion in revenue from selling those medicines from 2001 to 2008.

The total of \$2.75 billion Pfizer has paid in off-label penalties since 2004 is a little more than 1 percent of the company's revenue of \$245 billion from 2004 to 2008.

Lilly already had a criminal conviction for misbranding a drug when it broke the law again in promoting schizophrenia drug Zyprexa for off-label uses beginning in 1999. The medication provided Lilly with \$36 billion in revenue from 2000 to 2008. That's more than 25 times as much as the total penalties Lilly paid in January.

Companies regard the risk of multimillion-dollar penalties as just another cost of doing business, says Lon Schneider, a professor at the University of Southern California's Keck School of Medicine in Los Angeles. In 2006, he led a study for the National Institute of Mental Health of off-label use of drugs, including Zyprexa.

"There's an unwritten business plan," he says. "They're drivers that knowingly speed. If stopped, they pay the fine, and then they do it again."

Paying the doctors

In pushing off-label use of drugs, companies find ready and willing partners in physicians. Under the fragmented system of U.S. medical regulation, it's legal for doctors to prescribe FDA-approved drugs for any use. The FDA has no authority over doctors, only over drug companies, regarding off-label practices. It's up

to the states to oversee physicians.

"I think the physician community has to take some ownership responsibility and do their own due diligence beyond the sales and marketing person," says Boston's former U.S. Attorney Michael Sullivan.

Doctors generally don't tell people they're prescribing drugs pitched to them by pharmaceutical salespeople for unapproved treatments, says Peter Lurie, former deputy medical director of Public Citizen, a Washington-based public interest group. Most doctors don't keep track of FDA-approved uses of drugs, he says.

"The great majority of doctors have no idea; they don't even understand the distinction between on- and off-labeling," he says.

Pfizer's marketing program offered doctors up to \$1,000 a day to allow a Pfizer salesperson to spend time with the physician and his patients, according to a whistle-blower lawsuit filed by John Kopchinski, who worked as a salesman at Pfizer from 1992 to 2003.

"By 'pairing up' with a physician, the sales representative was able to promote over a period of many hours, without the usual problems of gaining access to prescribing physicians," Kopchinski says. "In essence, this amounted to Pfizer buying access to physicians."

Pfizer spokesman Chris Loder says the company stopped what it calls "mentorships" in 2005. He says Pfizer paid doctors \$250 a visit. The goal was clear: Get doctors to prescribe a new drug as widely as possible.

Pfizer's Neurontin is a case in point. The FDA approved the drug as a supplemental medication to treat epilepsy in 1993. Pfizer took in \$2.27 billion from sales of Neurontin in 2002. A full 94 percent -- \$2.12 billion -- of that revenue came from off-label use, according to the prosecutors' 2004 Pfizer sentencing memo.

Since 2004, companies that are now Pfizer divisions have pleaded guilty to off-label marketing of two drugs. Pfizer continued off-label promotions for these medications after buying the firms, according to documents.

Pfizer first stepped into an off-label scheme in 1999, when it offered to buy Warner-Lambert, based in New Jersey. Prosecutors charged that Warner-Lambert marketed Neurontin off-label between 1995 and 1999.

Warner-Lambert admitted doing so for one year in a May 2004 guilty plea for which Pfizer paid \$430 million in fines and penalties.

When the FDA approved Neurontin in 1993 to be used only along with other epilepsy drugs, the agency wrote that as a side effect, the drug can induce depression and suicidal thoughts in patients.

The whistle-blower

Much of what prosecutors learned about Warner-Lambert's marketing of Neurontin comes from a former employee, David Franklin, who holds a Ph.D. in microbiology.

Franklin, 48, whose title at Warner-Lambert was medical liaison, says his job involved more salesmanship than science. He told doctors that Neurontin was the best drug for a dozen off-label uses, including pain relief, bipolar disease and depression.

"Technically, I had responsibility for answering physician questions about all of Parke-Davis's drugs," Franklin says. "In practice, my real job was to promote Neurontin for off-label indications heavily -- to the exclusion of just about everything else."

Franklin says he knew such uses of the drug had no scientific support for effectiveness and safety.

"I was actually undermining their ability to fulfill the Hippocratic oath," Franklin says, referring to a physician's pledge to "First, do no harm."

After working for Warner-Lambert for three months, Franklin quit and filed a whistle-blower lawsuit on behalf of taxpayers to recover money the government paid for illegally promoted drugs. He stood to collect as much as 30 percent of any settlement the company made with the government.

Franklin had to wait four years -- until 2000 -- before the Justice Department began a criminal investigation. In November 1999, Pfizer made its public offer to buy Warner-Lambert. In January 2000, a federal grand jury in Boston issued subpoenas to Warner-Lambert employees to testify about the marketing of Neurontin.

That March, Warner-Lambert's annual report disclosed that prosecutors were building a criminal case. Undeterred, Pfizer bought Warner-Lambert in June for \$87 billion -- the third-largest merger in U.S. history.

More sales than Viagra

A year after the acquisition, the FDA discovered that Neurontin was still being marketed off-label. In a June, 2001 letter to the company, the agency wrote that Pfizer's promotion of the drug "is misleading and in violation of the Federal Food, Drug and Cosmetics Act."

Pfizer marketed Neurontin off-label after receiving that letter, agency records show. For 2001, Pfizer reported revenue of \$1.75 billion from Neurontin sales, making it the company's fourth-largest-selling drug that year, ahead of impotence pill Viagra, which Neurontin topped for four years.

As Neurontin sales soared to \$2.27 billion in 2002, the FDA found that Pfizer was improperly claiming that the drug was useful for a broader range of brain disorders than scientific evidence had established.

The agency sent a letter dated July 1, 2002, that said the company's marketing practices were in violation of FDA rules. It asked Pfizer to stop using misleading promotions. Pfizer reported \$2.7 billion in revenue from Neurontin in 2003. Overall, the drug has provided Pfizer with \$12 billion in revenue.

Pfizer spokesman Chris Loder says, "Regarding the 2001 and 2002 FDA letters, we do not believe that they were suggestive of any continuing off-label promotion."

For blowing the whistle on his employer, Franklin collected \$24.6 million under the False Claims Act.

Prosecutors Loucks and Sullivan got involved in the case after Franklin filed his suit, relying on information from Franklin and their own investigation. Before 2004, prosecutions for off-label marketing were rare.

"Until a couple of these cases became public, companies were probably saying, 'Everybody does it this way,'" Sullivan says.

Loucks had a track record in off-label prosecutions. In 1994, he negotiated a \$61 million settlement with C.R. Bard of New Jersey, which pleaded guilty to promoting off-label use of a heart catheter that led to patient deaths.

The off-label campaign

In the January 2004 settlement negotiations with Loucks, Sullivan and two other prosecutors, Pfizer's lawyers assured the U.S. Attorney's Office that the company wouldn't market drugs off-label.

"They asserted that the company understood the rules and had taken steps to assure corporate compliance with the law," Loucks says. "We remember those promises."

What Pfizer's lawyers didn't tell the prosecutors was that Pfizer was at that moment running an off-label marketing promotion using more than 100 salespeople who were pitching Bextra, according to a Pfizer sales manager who pleaded guilty to misbranding a drug in March 2009.

Pharmacia & Upjohn developed Bextra, which was approved by the FDA in 2001 for only the treatment of arthritis and menstrual discomfort.

P&U and Pfizer had by then crafted a joint marketing agreement to sell the drug. In November 2001, Mary Holloway, a Pfizer Northeast regional manager, began illegally training and directing her sales team to market Bextra for the relief of acute pain, Holloway admitted in the plea.

On Dec. 4, 2001, Pfizer executives sent Holloway a copy of a nonpublic FDA letter to the company. The agency had denied Pfizer's application to market Bextra for acute pain. Clinical trials had shown Bextra could cause heart damage and death.

Pfizer bought Pharmacia & Upjohn in April 2003. From 2001 through 2003, P&U, first as an independent company and then as a unit of Pfizer, paid doctors more than \$5 million in cash to lure them to resorts, where salespeople illegally pitched off-label uses for Bextra, P&U admitted.

In her guilty plea, Holloway said her team had solicited hospitals to create protocols to buy Bextra for the unapproved purpose of acute pain relief. Her representatives didn't mention the increased risk of heart attacks in their marketing.

They told doctors that side effects were no worse than those of a sugar pill, Holloway said.

In 2003, Holloway reported her unit's off-label promotions of Bextra up the corporate ladder at Pfizer, according to a presentencing memo to the judge written by Robert Ullmann, Holloway's attorney. Top managers didn't attempt to halt the illegal conduct, the memo said.

By late 2004, Bextra reached blockbuster status, with annual sales of \$1.29 billion. Holloway promoted Bextra until the FDA asked Pfizer in April 2005 to pull it from the market for all uses.

The agency concluded that the drug increased the risk of heart attacks, chest infections and strokes in cardiac surgery patients. In June 2009, Holloway, 47, was sentenced to two years on probation and fined \$75,000. She didn't return phone calls seeking comment.

'We regret . . . '

By 2007, the criminal and civil cases against Pfizer, its employees and its subsidiaries had begun to mount. The tally of drugs cited by federal prosecutors for off-label promotion reached six by 2009. In April 2007, P&U pleaded guilty to a felony charge of offering a \$12 million kickback to a pharmacy benefit manager. Pfizer paid a criminal fine of \$19.7 million. In September 2009, Pfizer agreed to pay \$2.2 billion in fines and penalties. P&U pleaded guilty to a felony charge of misbranding Bextra with the intent to defraud. After the settlement, Pfizer general counsel Amy Schulman said the company had learned its lesson.

"We regret certain actions we've taken in the past," she said. "Corporate integrity is an absolute priority for Pfizer."

One reason drug companies keep breaking the law may be because prosecutors and judges have been unwilling to use the ultimate sanction -- a felony conviction that would exclude a company from selling its

drugs for reimbursement by state health programs and federal Medicare.

At Pfizer's Pharmacia sentencing in October, U.S. District Court Judge Douglas Woodlock said companies don't appear to take the law seriously. "It has become something of a cost of doing business for some of these corporations, to shed their skin like certain animals and leave the skin and move on," he said.

As prosecutors continue to uncover patterns of deceit in off-label marketing, millions of patients across the nation remain in the dark. Doctors often choose the medications based on dishonest marketing by drug company salesmen.

Loucks says that putting an end to the criminal off-label schemes will be difficult. As drugmakers repeatedly plead guilty, they've shown they're willing to pay hundreds of millions of dollars in fines as a cost of generating billions in revenue.

The best hope, Loucks says, is that drug companies actually honor the promises they keep making -- and keep breaking -- to obey the law of the land.

As much as \$100 million for health-care fraud enforcement is tied up in the stalled reform legislation, according to Loucks.

"It will be increasingly hard for the threat of exclusion to seem credible and thus serve as a deterrent to bad corporate behavior," he says, "unless Congress supports health-care fraud prosecutions with more money."

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