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Late move on drugs by Bush FDA could be dangerous

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CORNELIUS, N.C. — In the waning days of the Bush administration, the Food and Drug Administration finalized new guidelines to make it easier for drug manufacturers to promote "off-label" prescription drug uses, which can be deadly for patients.

The move came despite criticism from Bush's own Department of Veterans Affairs, which said the change "favors business interests over public safety" and could lead to a "decline in drug safety." It also was crafted despite efforts by state and federal law-enforcement experts to clamp down on off-label drug marketing.

The new guidelines were issued four years after Robin Briggs of Cornelius, N.C., buried her husband, Doug, who committed suicide on a chilly Christmas Day after taking a drug off-label.

Doug Briggs, himself a physician, had taken a drug that the FDA had approved to treat epilepsy to ease his persistent back pain. It didn't do much for his back, but Robin Briggs said the drug's risk of producing suicidal behavior led to his death.

As the Obama administration reviews all the midnight rules that the departing Bush administration issued, it will have to decide whether to try to modify or reverse this last-minute change in the FDA's oversight of off-label drug marketing.

Congressional leaders from both parties criticized the guideline when it was proposed last year. Sen. Charles Grassley, an Iowa Republican who's repeatedly investigated the FDA, said he had serious concerns about the proposal, which he said would deem appropriate something that "the FDA once considered evidence of unlawful marketing."

"A legislative fix may be in order," Grassley said Thursday.

In the House of Representatives, Rep. Henry Waxman, a California Democrat, called the guideline a "long-coveted parting gift" for the pharmaceutical industry that "fundamentally undermines" the FDA's authority.

The use of drugs "off-label" — for reasons the FDA hasn't approved — has long been tolerated, and sometimes encouraged. For certain ailments, it can be helpful.

The practice also can be dangerous, however. Nearly every drug has side effects, some of them serious. Those risks can be worth the potential benefit that comes with an FDA-approved, on-label use. With an off-label use, however, the risks remain but the benefits are far less certain.

While it's legal for physicians to prescribe drugs off-label — often based on their reading of the latest medical research — it's illegal for drug makers to push such uses.

Over the past five years, federal prosecutors and state attorneys general have brought more than a dozen cases against drug makers for off-label marketing and won more than $6 billion in criminal and civil settlements, according to the Government Accountability Office and the U.S. Department of Justice.

In January alone, two of the nation's largest drug makers — Pfizer Inc. and Eli Lilly and Co. — said they'd agreed to two of the biggest off-label settlements ever.

"The FDA has been abysmal policing this area," said Connecticut Attorney General Richard Blumenthal, who helped engineer a major off-label case against drug maker Cephalon Inc. "One reason the states have been more and more active is that the federal government has been asleep at the switch."

Cephalon's case is illustrative.

At the start of the decade, Cephalon was a relatively small drug maker, and its three main drugs had limited audiences: for epilepsy, for the sleep disorder narcolepsy and for cancer pain.

So the company launched a "highly organized" and "concerted plan to maximize revenue by the off-label marketing" of the drugs, Gabitril, Provigil and Actiq, according to the government's trial memorandum. The off-label marketing "was no accident . . . . The very top levels of the company knew and approved of these efforts," the memorandum says.

Cephalon sales representatives were trained to encourage off-label marketing, sweet-talking doctors at lavish resort gatherings and rewarding them with consulting contracts, prosecutors said. Their income was dependent on high off-label sales.

Actiq, for example, was designed for cancer patients with extreme pain. Cephalon told its sales staff to pitch the powerful drug to general practitioners, not just to cancer specialists.

"Any patients suffering from moderate to severe episodic pain due to migraine headaches, sickle-cell pain crises, etc., are potential

candidates for Actiq," a 2002 sales strategy said.

It paid off. "The sales of Actiq doubled, tripled, quadrupled. As much as 80 percent of the sales of Actiq were off label," said Laurie Magid, the acting U.S. attorney in Philadelphia.

The epilepsy drug Gabitril was pitched to psychiatrists, who usually wouldn't prescribe an epilepsy drug; Cephalon management told sales reps that it was "VITAL to develop MORE psychiatry writers, MORE psychiatry adopters."

Each of the drugs had side effects, some of them strong. Actiq, for example, could depress breathing, causing death.

Cephalon was featured in a 2003 series of stories by Knight Ridder Newspapers — which McClatchy since has acquired — about the dangers of off-label drug use. A Knight Ridder analysis found that 21 percent of all prescriptions nationwide were for off-label uses, a figure that other researchers since have replicated. For some drugs — including those Cephalon sold — off-label use was far higher.

Magid's office went after Cephalon for violating drug-marketing laws and prompting fraudulent claims to government health programs such as Medicaid. Last September, her office announced that Cephalon would plead guilty to violating drug-marketing laws and pay $425 million in fines and other penalties.

While Magid and other prosecutors cracked down, however, the FDA relaxed its stance.

In its final week, the Bush administration opened the door to some off-label marketing. In what's called a "guidance" document, the FDA specified how drug companies could hand out medical journal articles that highlight potential off-label drug uses.

The guidance was complicated, and the main players in the issue still disagree about what it means for FDA oversight of off-label marketing. The drug industry generally endorsed the guidance as helpful to doctors and patients. The Washington Legal Foundation, which has accused the FDA of overstepping its authority, said that any FDA involvement in the issue was an unfair restriction on free speech and that drug makers should be free to share off-label information with doctors.

Health advocacy groups, insurers and state prosecutors, however, said the change would do more harm than good.

To be sure, doctors can find good information on new drug uses by reading medical journals. The screening process for medical journals, however, is rarely as rigorous as the FDA's drug approval process is. Without proper oversight, drug makers can pay for flimsy research on off-label uses and then use the results to promote their drugs.

The Bush FDA issued the new guidance over the objections of Bush's Department of Veterans Affairs, which pays for drugs taken by its health-system patients.

"We urge the FDA to withdraw" the proposal, the VA wrote the FDA last year. "It will not improve drug safety and could very well result in a decline in drug safety." Among other things, the VA said, "second-rate 'studies' published in journals with questionable peer-review processes will be used to convince physicians to use drugs for an ever-increasing number of unapproved uses."

Two researchers writing in the Journal of the American Medical Association echoed those comments, saying that medical literature is often the victim of manipulation.

Beyond that, the attorneys general of Illinois and Oregon complained of a "disturbing pattern" of drug companies "aggressively building market share based largely on off-label marketing campaigns that rely on widespread distribution of selected articles." The FDA, they argued, should boost oversight, not lessen it.

The FDA's Jarilyn Dupont said the agency tried to strike a balance between patients' interests and the medical community's free-speech rights.

"Doctors have the ability to read these articles on their own," she said. "So the question is, does it change the article if they are given it by a drug representative or they read it in a medical journal? The article is still the same."

Doug Briggs, the North Carolina doctor who committed suicide on Christmas Day 2004, sought out those kinds of articles himself; his evening routine, his wife said, was to retreat to the den after dinner to read the latest medical journals.

Even so, he still managed to get caught up in one of the most notorious off-label scandals in recent years.

He took a drug called Neurontin, which was developed and marketed by a company eventually bought by Pfizer, the world's largest drug maker. In 2004, the Pfizer division agreed to pay $430 million to settle criminal and civil cases about off-label marketing of Neurontin.

At times, 90 percent of Neurontin's sales were off-label, and much of that was for patients such as Doug Briggs, who'd been prescribed the drug by an orthopedic specialist.

"We were firm believers in pharmaceuticals," said Robin Briggs, who's a nurse. "We were a medical family."

The drug didn't help the pain, his family said, but it did change his demeanor. He became moody and easily agitated. On Christmas Day, he urged his wife and two adult sons to go out for a movie. When they came back, the house was dark.

Briggs had hanged himself, leaving only a cursory note. His younger son was the first to find him.

Federal officials have since told Pfizer and other makers of anti-epilepsy drugs to add suicide risk warnings to their drugs' packaging labels. Robin Briggs has sued Pfizer and the maker of a generic version of the drug; that case is pending.

Pfizer, in a statement, said the "allegations in this case are simply not supported by the very considerable scientific evidence and clinical data related to Neurontin."

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