CURBING THE DRUG MA

How a clampdown on pitching drugs for unapproved uses is changing the way Big Pharma operates

By DAREN FONDA and BARBARA KIVIAT

EMPATHIZING WITH THE DRUG INdustry may be tough these days, especially if you just emptied your wallet to pay for your prescription or rode a Greyhound to Canada to buy the same medicine for less. But just for a moment, put yourself in the shoes of pharmaceutical executives who last week attended a conference in Boston on the latest practice to tarnish their trade: the sale and illegal marketing of drugs for "off label" uses not approved by the FDA. "Rarely has a conference been more timely," warned James Dillon, a partner at Foley Hoag, the Boston-based law firm that sponsored the event. Prosecutors and regulators are circling, the executives were told. Would-be whistle-blowers are collecting promotional materials, saving e-mails, taping phone calls—in the hope of sharing in a jackpot settlement. A PowerPoint slide at the conference showed a kitten (representing the drug industry) in front of a row of German shepherds (the federal regulators), unleashed and ready to pounce.

The notion of Big Pharma cowering before the feds is a bit of a stretch, considering its army of lobbyists encamped in Washington—a total of 526, about one for every member of Congress, according to a report issued last week by the watchdog group Public Citizen. Despite the siege mentality at the con-

Illustration for TIME by Zohar Lazar

$2 billion
Amount pharmaceutical companies have agreed to pay the U.S. since 2001 to settle allegations of illegal sales and marketing practices

93%
Increase in total spending on pharmaceutical promotion in the U.S. from 1997 to 2002

66%
Increase in spending on domestic R. and D. in the same period

59%
Increase between 1995 and 2000 in marketing staff at brand-name drug companies

2%
Decrease between 1995 and 2000 in R. and D. staff at brand-name drug companies

1 to 2
Approximate ratio of drug-sale reps to physicians who actively write prescriptions

Sources: Ernst & Young; IMS Health; PhRMA; Alan Sager at Boston University

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ference—and fears of a shortage of blockbusters in the pipeline just as several billion-dollar drugs get ready to come off patent—the industry remains one of America's healthiest. U.S. prescription-drug sales grew 11.5% last year, to $216 billion; the top 10 pharmaceutical firms netted a combined income of some $50 billion; and drug companies booked average profit margins of 14%, among the highest of any U.S. industry.

Yet two recent cases involving off-label sales of prescription drugs, Neurontin and Paxil, are rekindling debate about whether drugmakers are generating profits at the expense and health of consumers. Since 2001, pharmaceutical companies have paid the U.S. government more than $2 billion to resolve charges of fraudulent sales and marketing tactics (including a record $875 million that TAP Pharmaceutical Products paid as a settlement in 2001 over kickback schemes to get doctors to prescribe its prostate-cancer drug Lupron). Almost every major firm is now being investigated. Says T. Reed Stephens, a former federal prosecutor who brought several cases against Big Pharma: "We've got a *Titanic* situation here. What we don't see is the rest of the iceberg."

Prescribing drugs for off-label uses is nothing new, nor is it illegal. Doctors have been doing it for decades to treat rare diseases, pediatric disorders (for which medicines are often not specially approved) and various cancers. By some estimates, more than half of all oncology patients are treated with at least one off-label drug as part of their chemotherapy regimen. And many doctors see the practice as life-saving science. Statins, for example, were initially approved to lower cholesterol but are now heavily prescribed (and blessed by regulators) to prevent heart attacks and stroke. Says Dr. Cary Gross, assistant professor of medicine at Yale: "You can't tell doctors never to try anything except what's been tested." Since 1998, the number of off-label prescriptions has nearly doubled, to around 115 million, according to an analysis by Knight Ridder Newspapers.

But promoting drugs for off-label use is illegal, and it's now clear that illicit marketing fueled some of that growth. "I talked off-label all the time," says a former drug rep who worked at Merck in the 1990s, claiming that he would often take his boss's advice—"if you're not in trouble, you're not working"—and break with official company policy to distribute literature about off-label uses to doctors. (A Merck spokeswoman says the company "strives to maintain the highest standards in marketing our medicines in full compliance with FDA regulations.")

For sheer nerve, it would be hard to beat the sales force at Warner-Lambert (bought by Pfizer in 2000), which came up with ingenious ways of promoting off-label uses for Neurontin, a drug initially approved only for treating epilepsy, a relatively small market. In the 1990s, according to whistleblower David Franklin, Neurontin salesmen paid doctors to prescribe the medicine for ailments ranging from manic depression to restless-leg syndrome—though the company had evidence that the drug was ineffective for some of those ailments. The firm hired ghostwriters to draft articles promoting off-label uses and then shopped around for doctors to lend their names as authors for $1,000 "honorariums." "It's so wrong," says Regina Adams, who took Neurontin for manic depression and attempted suicide while on the drug. "They don't care about the victims, about what it does to people who are on it."

Neurontin sales came in at $2.7 billion last year—with off-label prescriptions accounting for an estimated 90%. But Pfizer is paying dearly for those sales. Last month its Warner-Lambert division agreed to plead guilty and pay $430 million to resolve civil and criminal charges stemming from the fraudulent sales tactics. Under a federal whistle-blower law, Franklin earned a $26.6 million share of the settlement. Pfizer, meanwhile, says it never saw the kinds of practices that Warner-Lambert engaged in from its own sales force. "Pfizer's approach is proactive," says a company spokesman. "We've got good products and want to promote them in the appropriate ways."

By most accounts, the hard-sell tactics used by Warner-Lambert and other drugmakers have tapered off. Experts say the lawsuits have helped, as has muscle flexing by regulators and a new set of ethics guidelines. In 2000 the American Medical Association launched a campaign to try to curtail freebies and kickback schemes (no more golf outings to Bermuda or Super Bowl tickets, and no more of the infamous "gas and go," in which drug reps would chat up doctors at gas stations while they filled their tanks). The drug industry's trade group, PhRMA, produced similar guidelines in 2002.

At Schering-Plough, under investigation by the Justice Department for off-label marketing, CEO Fred Hassan says compliance has to become "part of the DNA" of a drug company. Since Hassan took office last year, his efforts to crack down on unethical sales pitches have included factoring "business integrity" into the reps' bonuses. The company has also instituted an "integrity hot line" for employees' anonymous tips as well as a chief compliance officer who reports directly to the CEO and the board of directors—instead of the legal department, which used to be the standard industry practice.

Yet industry veterans argue that it

DRUG TESTING

Putting Trials on the Record

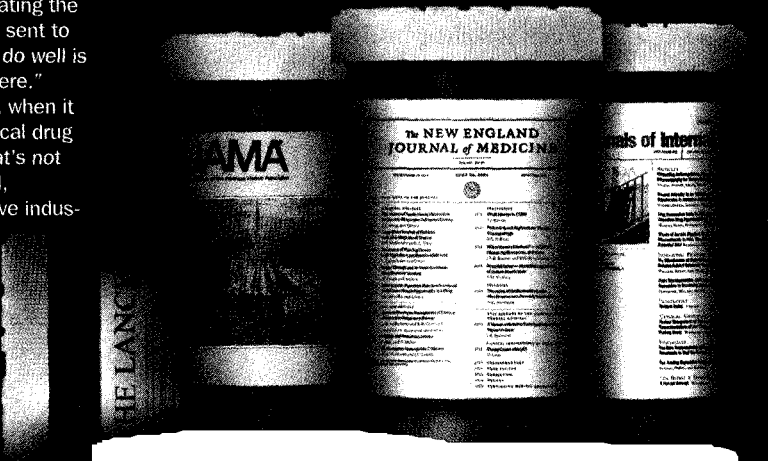
Peer-reviewed journals wield enormous power in the pharmaceutical industry. A study published in one of the more prestigious—the *New England Journal of Medicine (N.E.J.M.)*, say, or the *Journal of the American Medical Association (J.A.M.A.)*—can make or break a new drug. But the journals are far from perfect. One big problem, says Dr. Drummond Rennie, a *J.A.M.A.* editor, is that "while journals are very good at evaluating the significance of studies sent to them, what they don't do well is evaluate what's not there."

And unfortunately, when it comes to data on clinical drug trials, there is a lot that's not there. Why? First of all, researchers who receive industry funding don't necessarily get to decide whether the results are submitted for publication. Many researchers also practice a form of self-censorship in an effort to please their sponsors or in mistakenly believing that journals tend to favor positive results. Others will cherry-pick a narrow slice of data for publication while consigning the rest to the file drawer. Whatever the reason, the result is a bias against negative or inconclusive data that distorts the medical literature and ultimately the practice of medicine.

And that's why there is a movement afoot to require researchers to register all clinical trials when they start. This isn't a new idea, but it's been given new urgency by, among other cases, the example of GlaxoSmithKline (GSK) and its antidepressant Paxil. While data that showed Paxil could help depressed adolescents were published in the *Journal of the American Academy of Child & Adolescent Psychiatry*, the results of another trial, which raised concerns about children having suicidal thoughts while on Paxil, were not submitted for publication. (GSK points out, however, that the negative results were presented at a major medical meeting.)

A registry won't mean that every failed trial will be published, but it will make it clear that those trials took place. The International Committee of Medical Journals, which includes *J.A.M.A.* and *N.E.J.M.*, is drafting plans for a registry system, and the A.M.A. has a proposal on the table. Doctors met last week with Democratic lawmakers who are considering legislation that would require disclosure of results. Meanwhile, some drugmakers, among them GSK and Merck, have indicated that they are more inclined to back the trend than to buck it.

The prospect of having data from all clinical trials readily available is exciting, says Dr. Cary Gross of Yale: "This has the potential to dramatically change how medicine is practiced." But just as compelling is the ethical argument. "When people enroll in a study, they are told that this is going to benefit science," says Gross. "For trials results to then be shelved is a real betrayal of people who have trusted researchers with their lives." The pharmaceutical industry would be well advised to see it that way too. —*By David Bjerklie*



would be naive to think that drug manufacturers won't continue to promote their medicines for off-label uses. Too much money is at stake. According to industry estimates, it costs around $800 million to bring a drug to market, and once the drug is approved for one use, the race is on to profit from the investment before the patent expires. Moreover, the lines between science and promotion seem to be blurring in the business of continuing medical education (CME), which is required for physician-license renewals. Between 1993 and 2001, medical-school funding for CME dropped 41%, while industry support soared 188%, now accounting for 60% of the total. Says Dr. A. Mark Fendrick, a professor of medicine at the University of Michigan: "Let's face it, industry funding is the lesser of two evils."

One consequence: conflicts of interest, according to Dr. Jerome Kassirer, a former editor of the *New England Journal of Medicine* and author of the forthcoming book *On the Take: How Medicine's Complicity with Big Business Can Endanger Your Health*. Kassirer points to a brochure, mailed to physicians last year, touting the benefits of a compound called EPO (erythropoietin) for treating anemia. Drugs containing EPO have been approved only to treat kidney disease and, in certain situations, cancer and AIDS. But after reading the brochure, he says, "only an idiot could walk away not thinking it would be useful to prescribe EPO" for off-label uses. Who funded the brochure? The National Anemia Action Council. And who funds the council? Amgen, the leading maker of EPO.

However the industry sorts out the off-label-use debate, more lawsuits (if not criminal charges) seem likely. New York attorney general Eliot Spitzer's suit against GlaxoSmithKline—for failing to widely publish negative studies of off-label uses of its antidepressant Paxil—may have opened a new legal line of attack. "You could conceive of people who weren't injured or hurt now filing suit," says Stephens, the former prosecutor. More lawsuits could also translate into higher costs for drug companies—and higher prices for drugs. And that's a headache no pill can cure. —***With reporting by David Bjerklie and Julie Rawe/New York, Stefanie Friedhoff/Ann Arbor, Eric Roston/Washington and Nathan Thornburgh/Boston***


JIM STEM—SILVER IMAGE FOR TIME

THE VICTIM Adams says she was harmed by drug-company sales tactics