Another belated disclosure from the pharmaceutical industry

Cholesterol-lowering drug linked to increased risk of heart attack

Naomi Spencer
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Under pressure from media reports, consumer groups and federal investigators, pharmaceutical giant Merck and its partner Schering-Plough released the findings of a long-withheld company-sponsored study of the cholesterol-lowing drug Zetia this week. The study, completed in April 2006, reveals that companies had been falsely marketing the drug as an effective part of heart disease prevention. Moreover, the data indicate a link between the drug—taken by about a million Americans—and increased risk of heart attacks and strokes.

The revelation is the latest in a series of scandals in the pharmaceutical industry and yet another demonstration of the federal Food and Drug Administration's failure to protect the American people by ensuring the safety and efficacy of aggressively marketed medicines.

The so-called Enhance study was intended to demonstrate that Merck and Schering-Plough's Vytorin, a combination of Zetia and another cholesterol-lowering drug, Zocor, reduced the build-up of fatty plaque in the arteries in addition to lowering so-called bad cholesterol levels. Instead, data suggested the opposite: plaque built up in the arteries of patients on Vytorin at double the rate of those taking Zocor alone.

Zocor, along with Crestor, Lipitor, and other common cholesterol-lowering medicines, are known as statins. Statins work in the liver by blocking the formation of low-density lipoprotein cholesterol (LDL), or 'bad' cholesterol. Some research also suggests that statins can also reduce inflammation that may cause plaque to block or rupture heart arteries.

Zetia, by contrast, blocks LDL cholesterol absorption in the intestines. Previous studies have suggested that Zetia lowers LDL cholesterol levels in patients by 15 to 20 percent, and the recently released study found Vytorin lowered LDL levels in patients by 58 percent. However, as Steven Nissen, chairman of cardiovascular medicine at the Cleveland Clinic, commented to *Time* magazine January 15, "The bottom line is that we just don't know what Vytorin does, because we don't have the clinical trials. We know Vytorin blocks absorption of cholesterol. But what else does it block—something else in the diet that could be beneficial? We just don't understand fully how it works."

A question naturally arises: How did a drug, the pharmacological qualities of which were not published and not understood, pass muster with federal regulators?

The FDA approved Zetia in 2002 and Vytorin in 2004, and through heavy marketing the drugs became extremely popular. According to health care industry tracker IMS Health, doctors wrote 18 million prescriptions for Vytorin and 14 million for Zetia in 2006 alone.

Cholesterol-lowering drugs represent a $40 billion global market; Zetia and Vytorin account for nearly $5 billion in annual sales. Worldwide, nearly a million prescriptions are written each week for the drugs.

Beyond the Enhance study results, there are a number of other, less-publicized problems surrounding the drugs and their marketing.

When the FDA approved Zetia for sale, it accepted company drug trials that covered a relatively small number of patients, and lasted no longer than 12 weeks—a short term for drug testing. Yet, according to a December 21 report from the *New York Times* based on FDA documents, even the data from those limited trials suggested that Zetia posed dangers when taken along with statins.

The *Times* said 11 times as many people who took a Zetia and statin combination subsequently suffered serious health problems compared to those who took only a statin. Nearly all of those complications were liver-related. Yet the FDA regarded the risks, according to the paper, as "relatively minor," approving the drug without requesting Merck-Schering-Plough to conduct longer trials.

Two years later, the FDA approved Vytorin against the recommendations of its own pharmacology reviewer, who warned that tests in laboratory animals had registered serious toxicity even in small amounts.

The *Times* also found references in FDA briefing papers to eight long-term studies of Zetia in combination with statins, conducted by Merck and Schering-Plough between 2000 and 2003. The FDA documents show that several other long-term trials were conducted involving thousands of patients, but the companies did not release the results.

The companies published only three of their studies, mostly covering short periods in which it was not possible to detect the development of liver problems. According to the *Times*, Schering-Plough vice president Robert Spiegel confirmed the existence of the studies but said they were not "scientifically important enough" to be published. "We're pretty comfortable that people don't have trouble tolerating Zetia," he told the paper.

The drugs are sold in the US with only minimal warnings of potential liver damage. In Australia and Canada, however, regulators have issued warnings since 2005 about Zetia's potential to cause hepatitis and pancreatitis.

A Schering-Plough spokesperson confirmed to the *Times* that some patients had been dropped from the Enhance study after testing revealed that they had "elevated liver enzymes," suggesting that the

newly released data may also yield evidence of Zetia's risks to the liver.

The conduct of the companies and the FDA play like a repeat performance of the Vioxx scandal. Vioxx, Merck's pain medication, was propelled by an ad campaign touting its potency as an arthritis pain reliever without the adverse side effects on the digestive system that can be caused by common medicines such as ibuprofen. The drug was used by more than 2 million people worldwide.

In 2000, just a year after its introduction on the US market, results of a large clinical trial suggested that Vioxx posed much greater risks, including the risk of increased heart attacks, than older painkillers on the market. Merck disputed the findings, only withdrawing the drug in 2004, after another clinical trial definitively linked Vioxx to increased heart attacks and strokes. Internal company documents subsequently revealed that Merck researchers had warned of the risks several years before. Likewise, whistleblowers within the FDA warned that tens of thousands of Vioxx patients had suffered heart attacks, but the agency lacked the authority and the will to issue regulations on the drug.

Nor is Vioxx the only similar case. In 2006, the antibiotic Ketek (telithromycin), marketed by French pharmaceutical Sanofi-Aventis, and prescribed more than 5 million times in two years, was found to have submitted fraudulent data to the FDA masking potentially fatal liver risks. The agency was flooded by voluntary patient reports of adverse reactions, leading David Graham, head of the FDA's drug safety office, to say that federal approval of the drug had been a mistake and recommend the drug's "immediate withdrawal."

"It's as if every principle governing the review and approval of new drugs was abandoned or suspended where telithromycin is concerned," Graham wrote in a June 16, 2006, e-mail obtained by the *New York Times*. "We don't really know if the drug works; no one is claiming it works better than other, safer drugs; and we're flying blind as far as safety goes, except for our own A.D.R. [adverse drug reaction] data that suggests telithromycin is uniquely more toxic than most other drugs."

In May 2007, the *New England Journal of Medicine* published an analysis of more than 40 clinical studies of the diabetes drug Avandia, produced by pharmaceutical giant GlaxoSmithKline. The journal's findings suggested Avandia raised the risk of heart attack by 43 percent, and the risk of cardiovascular death by a staggering 64 percent. FDA officials responded by saying that the agency was postponing a decision on the drug's safety for two years, despite its own estimate that as many as 60,000 to 100,000 heart attacks may have been linked to Avandia during its eight years on the market.

All of these instances are the result of the subordination of public health to corporate profits. Medicine under capitalism is inherently compromised by this conflict of interest, putting millions of ordinary people at risk for companies' bottom lines.

In September, the FDA Revitalization Act was signed into law, ostensibly strengthening the agency's oversight powers. The legislation enables the FDA to require post-marketing drug safety tests and changes to labeling. The FDA now also has the authority to "request" changes to television ads for drugs aimed at consumers.

The law also requires sponsors of all clinical drug trials to register the studies in a public database managed by the National Library of Medicine. Yet, as the numerous as-yet undisclosed Zetia trials exemplify, the law is meaningless if it is not enforced.

Significantly, the new law reauthorized the 1992 system of fees whereby the FDA's drug review process is largely funded by corporations submitting their products for approval. The FDA's safety division is heavily dependent upon corporate money for lack of federal funding.

According to the consumer advocacy group Public Citizen, the pharmaceutical industry gave $400 million to the drug division of the FDA. "You would have to be living on a cloud to think that the money doesn't have an impact on the FDA's drug approvals or regulation of the industry," Sidney Wolfe, the group's Health Research director, commented in a statement January 14.

In addition, the new law does not substantively address the relations between the pharmaceutical industry and doctors. Drug companies establish a market in large part by establishing relationships with physicians through gifts and perks.

These gifts are regulated only by voluntary industry guidelines and justified on the basis that corporate sales representatives provide vital information to medical practitioners. The Pew Charitable Trust's Prescription Project found drug companies spend $7 billion on gifts to doctors and at least $18 billion on free samples for doctors' offices each year.

According to a report in the January issue of the *AARP Bulletin*, a publication of the American Association of Retired Persons, "Each day more than 101,000 drug company reps—one for every five office-based physicians—call on the nation's doctors." Citing a 2005 report by medical products industry consulting firm Health Strategies Group, the *AARP Bulletin* reported that "Primary care physicians, on average, have 28 interactions a week with drug reps." These representatives are paid to promote new drugs and downplay any side effects or risks.

The *Bulletin* noted that the drug industry is "vehemently opposed to marketing-disclosure legislation." Industry group Pharmaceutical Research and Manufacturers of America (PhRMA) calls such regulations "no extra value to patients" and "a costly, unnecessary burden" for drug companies. PhRMA senior vice president Ken Johnson told the *Bulletin* that "In the end, pharmaceutical marketing is one of several important ways for physicians to receive information they need to make sure patients are safely and effectively treated."