

Is the FDA On Drugs?

A TIME investigation of Avandia's journey from lab to pharmacy reveals serious flaws in the way the Food and Drug Administration protects consumers from harmful medicines

BY MASSIMO CALABRESI WITH ALICE PARK

FIVE DAYS BEFORE A 2007 ARTICLE in the *New England Journal of Medicine* showed that the diabetes drug Avandia was linked to a 43% increase in heart attacks compared with other medications or placebos, a group of scientists and executives from the drug's maker, GlaxoSmithKline (GSK), gathered in a conference room at the offices of the Food and Drug Administration in White Oak, Md. The GSK goal: to convince regulators that the evidence that the company's \$3 billion-a-year blockbuster drug caused heart problems was inconclusive. To do that, the GSK officials focused not on heart-attack data but on a broader, less well defined category of heart problems called myocardial ischemia. The most recent studies of Avandia, the GSK officials told the FDA, had "yielded information that is inconsistent with an increased risk of myocardial ischemic events," according to sealed court proceedings obtained by TIME.

What GSK didn't tell the FDA was that on May 14, 2007, two days before the White

Oak meeting, GSK's Global Safety Board had noted that a new assessment of Avandia studies "strengthens the [cardiac-risk] signal observed in the [previous] analysis." Or that eight days earlier, the company's head of research and development, Moncef Slaoui, had sent an e-mail to its chief medical officer saying Avandia patients showed an "increased risk of ischemic event ranging from 30% to 43%!" Or that the day before the meeting, the company had produced a preliminary draft report that showed patients on Avandia had a 46% greater likelihood of heart attack than those in a control group.

But the mixed-evidence argument GSK presented to the FDA worked. After months of deliberation, the agency decided to keep the drug on the market—a move worth billions of dollars to GSK but that also may have put millions of patients at risk.

Such examples of the drug industry's outmaneuvering FDA regulators are disturbingly common, say both scientists and policymakers who follow drug approval

and safety monitoring. More than 140 million Americans take at least one prescription drug in any given month, and they rely on the FDA to ensure those drugs are safe. That trust, the story of Avandia illustrates, is a gamble. In July, an FDA advisory group conducted the second hearing on the drug's safety since its 1999 approval and again concluded that the evidence against the drug was insufficient to pull it from the market. The group instead recommended additional warnings and restrictions on Avandia's use. In the coming weeks, the FDA will decide whether to take that advice or withdraw Avandia from the market.

Gaming the System

OVER THE PAST TWO DECADES, AS DRUG after drug has been recalled after winning FDA approval, it has been hard not to wonder if FDA regulators have been captured by the drug industry. FDA critics and industry monitors charge that the drug-approval process is too easy for

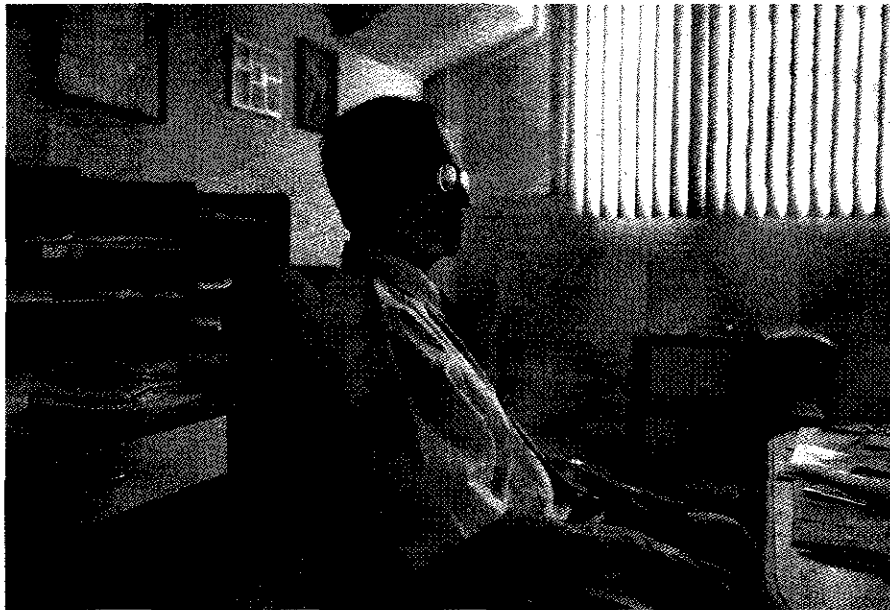
pharmaceutical companies to game. It is in some ways an unsurprising development. The FDA serves a public insatiably hungry for new medicines. Yet the agency does not have responsibility for performing safety testing. It relies on drug companies to perform all premarket testing on drugs for safety and efficacy. And it relies on industry "user fees" for 65% of its budget for post-market monitoring of the drugs it approves, thanks to a 1992 law designed to speed treatments to patients. "The FDA's relationship with the drug industry [is] too cozy," says Senator Chuck Grassley of Iowa.

Federal studies reveal that the FDA doesn't have a complete or accurate list of prescription drugs on the market and is missing or has incomplete information on one-third of the drug-safety and efficacy trials under way. Over the past three years, the inspector general at the Department of Health and Human Services found that the FDA had inspected only 1% of clinical-trial sites from 2000 to 2005 and lacked financial-disclosure data for clinical investigators in half of all industry drug reviews.

The results of this broken system may prove criminal as well as fatal. In June, FDA whistle-blower Dr. David Graham published an article suggesting that Avandia caused 47,000 more diabetics to suffer heart failure, stroke or death than would have been the case if they had taken an alternative. The risk is especially troubling given that diabetics are already more vulnerable to heart disease because of their condition. Congressional reports revealed that GSK sat on early evidence of the heart risks of its drug. Equally alarming is the revelation that the FDA knew of the dangers months before it informed the public. Now the FDA is investigating whether GSK broke the law by failing to fully inform the agency of Avandia's heart risks, deputy FDA commissioner Dr. Joshua Sharfstein tells *TIME*. At the least, the story of Avandia shows how drug companies use uncertainty to their advantage—at a risk to public health.

Risk and Reward

IN NOVEMBER 1998, SMITHKLINE BEECHAM (SB), which more than a year later would merge with Glaxo Wellcome to become GlaxoSmithKline, presented the FDA with an impressive application to market Avandia: dozens of boxes, each containing eight volumes the size of the New York City phone book, filled with trial data and chemical analyses. Avandia, or rosiglitazone, was only the second in a new class



Watchdog The FDA's Misbin first voiced concerns about Avandia-associated cardiac risks in 1999

of antidiabetes drugs that was showing promise in helping Type 2 patients keep their blood sugar in check. But the first product, troglitazone, or Rezulin, was also causing a troubling amount of liver damage, so doctors and patients were eager for a safer alternative. Aware of this, FDA officials put Avandia on a six-month fast track to approval. As the FDA's medical, statistical and pharmacological reviewers went through the mountain of documents, they soon found the same thing: Avandia users experienced more cardiovascular issues, including a rise in bad cholesterol (or LDL) and lipids, than those taking other antidiabetes medications or a placebo. But detailed though the pages of data provided by SB were, they didn't show this danger of heart problems with certainty.

In public, SB executives defended the safety of their drug. At an April 1999 FDA public hearing featuring outside experts charged with recommending whether to

approve Avandia, SB's head of research and development, Dr. Tadataka Yamada, maintained that Avandia had a "risk-neutral lipid profile" and "cardiovascular safety... comparable to placebo and active comparators." FDA scientists disagreed. Concerned about the boost in LDL, FDA pharmacologists recommended against approving the drug. Dr. Robert Misbin, the FDA's medical officer, said he would support approval only if the company committed to a thorough safety trial that would include monitoring for cardiovascular risks.

The hearing committee, three of whose eight voting members had declared financial conflicts of interest in the case, debated the heart issue and eventually recommended that the FDA approve the drug. (*TIME* requested the forms that waived the conflicts of interest; an FDA official declined to release them and said none of the conflicts involved a relationship with SB.) Then came the horse-trading. After outside experts weigh in on a new drug, but before it receives final approval from the agency, the FDA and the drugmaker negotiate which tests the company will perform once large numbers of people are taking it on the open market.

On May 5, 1999, SB sent its proposal for testing Avandia to the FDA. The company didn't want to do a long-term safety test at all. Less than a week later, in a letter to his superior, Misbin threatened to withdraw his approval recommendation, saying the risk of heart disease may be increased by

'Companies are always going to present their best face. It's our job to say no.'

—DR. ROBERT MISBIN, FDA MEDICAL OFFICER

DAVID Y. LEE FOR TIME

treatment with Avandia and accusing SB of attempting to divert attention from dangers that Avandia might pose to patients, according to parts of the letter read to TIME.

Then, right at the May 25 deadline for FDA approval, SB made an offer to focus its testing on the drug's ability, as compared with competitor drugs, to lower blood sugar. It was a side step from the question the agency wanted to answer about the drug's safety. Instead of focusing on finding out if Avandia posed a heart risk, SmithKline Beecham was going to run a trial its sales representatives could use to promote the drug. "It was really a marketing study," says Misbin now. But later that day, Dr. John Jenkins, the FDA's director for new drugs, accepted SB's proposal for testing the drug on the market and approved Avandia for sale. By agreeing to the company's version of the postmarket trial, scientists say, the FDA abdicated its responsibility to collect reliable data on Avandia's safety.

Even with the FDA's help, the company had its hands full. In 1999, Dr. John Buse of the University of North Carolina at Chapel Hill, a diabetes expert, using slides that SB officials had presented at their approval hearing, did his own calculations based on the data. In speeches, he highlighted the fact that Avandia users experienced a more than fourfold rise in cholesterol compared with those taking a placebo. Because elevated cholesterol levels are a risk factor for heart disease, Buse wrote to the FDA commissioner, warning that Avandia could cause "adverse cardiac outcomes." In March 2000, officials with the newly merged GlaxoSmithKline got a copy of the letter and, Buse tells TIME, contacted his boss, accusing Buse of being a liar and being for sale, and saying he needed to be muzzled. The company's stock had dropped, and "they threatened to sue me for something like \$4 billion, which was the loss of the company's valuation," he says.

In the meantime, the company took measures to promote Avandia. In 2001, GSK worked on an article, later published in the American Heart Association's journal *Circulation* by Dr. Steven Haffner of the University of Texas Health Science Center at San Antonio, arguing that the class of drugs that includes Avandia could significantly reduce cardiovascular risk factors in animals. At meetings with doctors in 2001, GSK sales representatives denied Avandia had cardiac side effects, prompting the FDA to issue a public letter of warning against the company.

Keeping the Public in the Dark

BY 2004, AVANDIA SALES WERE EARNING GSK more than \$1.5 billion a year in the U.S. alone. But as more people went on the drug, the picture on cardiovascular risk began to get clearer. GSK began a review of the drug's heart risks, and in 2005 and 2006 the company produced internal analyses showing 29% and 31% jumps in negative heart events. On May 9, 2006, the company provided these results to the FDA. The agency didn't immediately release those studies to the public, because its officials "didn't necessarily agree with some of the methodology used," says Dr. Janet Woodcock, head of the FDA Center for Drug Evaluation and Research. Instead, the FDA put its own statistician on the job. Just before Christmas that year, Misbin looked at the statistician's spreadsheet and found that "in virtually every trial, there were more cardiac events with Avandia than with the comparator," Misbin says. He was convinced enough to call his uncle, who was on Avandia, and advise him to ask his doctor to switch him to another drug.

It was seven years after the drug was approved, and the dangers of Avandia had still not been made sufficiently clear to the public. The FDA was sitting on the new analyses, and GSK, the FDA discovered during an investigation by its inspections unit in the fall of 2007, had failed to report clinical data and other material from 15 tests of Avandia by the end of 2006, according to a March 25, 2008, warning letter to the company. With the company and the FDA maintaining tight control over the full database of information on Avandia's effectiveness and safety, there was little independent scientists could do to assuage their growing concerns about the drug.

Then came a bit of legal serendipity. As part of a settlement with the state of New York over GSK's nondisclosure of possible heightened suicide risk among teenagers taking its antidepressant Paxil, the company agreed to put all its recent clinical studies on a website. Aware of the growing concerns among clinicians about the risks posed by Avandia, in April 2007, Cleveland Clinic cardiologist Dr. Steven Nissen Googled the site and downloaded all of the available Avandia trials. After analyzing the 42 trials, he wrote up his findings and in May submitted them to the *New England Journal of Medicine*. He had found what GSK and the FDA already knew: a 43% higher rate of cardiac events

FDA and Avandia. An 11-year odyssey

1998

NOV. 25

SmithKline Beecham (SB) submits an application to FDA for Avandia, a drug that helps control blood sugar in people with Type 2 diabetes

1999

APRIL 22

FDA reviewers report cardiovascular risks in Avandia

MAY 25

FDA approves Avandia for sale

2000

JANUARY

SB merges with Glaxo Wellcome to become GlaxoSmithKline (GSK)

2001

OCTOBER

Internal GSK study shows added risk of heart attack when Avandia is taken with other diabetes drugs

2002

APRIL

FDA requires warning labels about Avandia and cardiovascular health

2004

U.S. sales of Avandia reach \$1.5 billion

2006

MAY

GSK submits study to FDA finding a 31% increase in heart-attack risk

2007

MAY 15

GSK internal study shows a 46% increase in heart-attack risk

MAY 16

GSK tells FDA heart-risk data are inconsistent

MAY 21

Nissen article reports Avandia increases risk of heart attack 43%

NOVEMBER

FDA keeps Avandia on the market

2008

DECEMBER

Avandia's U.S. sales drop 49% from 2007's

2010

JUNE

FDA's Graham says 47,000 people suffered stroke, heart failure or death from Avandia

JULY 14

Majority of FDA panel says Avandia should stay on the market; a decision by the FDA chief is expected soon

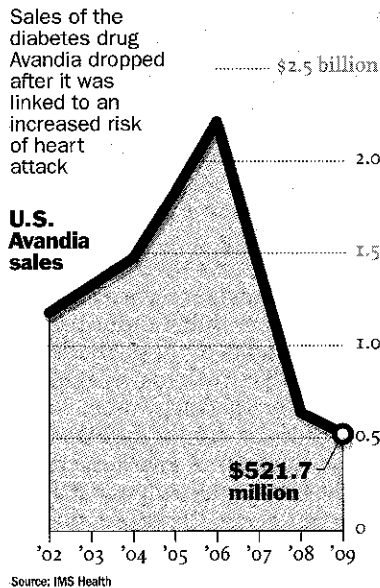
among Avandia patients compared with those taking other drugs or placebos.

By chance, the *New England Journal of Medicine* chose as a prepublication reviewer of the Nissen article Haffner, the University of Texas doctor who was the lead author on the 2001 paper that had suggested that Avandia's class of drug could decrease cardiovascular risk. He faxed a copy of Nissen's article directly to GSK. Now GSK faced the threat of broad public awareness of the hazards of its drug. So with the clock ticking until Nissen's article was to be published on May 21, 2007, GSK harvested data on cardiac events from the recently completed efficacy trial Jenkins had signed off on back in 1999. Because the trial had been designed to show efficacy, not safety, its cardiac data were inconclusive.

As it prepared for the pivotal May 16, 2007, meeting in White Oak with FDA regulators, GSK came up with an additional counterattack to Nissen's study. Unlike the FDA, European regulators had insisted on a long-term cardiac-safety study, called RECORD, when they approved the drug. So GSK argued that the only prudent approach would be to let the RECORD trial run to completion in 2009 to reach a definitive answer on cardiovascular risk. To top agency officials, it seemed like a reasonable solution at the time. But three years and hundreds of millions of dollars in Avandia sales later, it turns out the RECORD trial may not be as reliable a study of cardiac risk as agency officials had hoped.

Regulator, Regulate Thyself

BY 2008, AFTER THE PAINKILLER VIOXX and the cholesterol-lowering medication Baycol were pulled from the market because of side effects and complications, House and Senate overseers both began investigations of the drug-approval process and the relationship between the drug industry and its federal minders. The Senate Finance Committee concluded in January 2010, after a two-year review, that GSK failed to promptly alert the FDA about Avandia's drug risks. In response, FDA commissioner Dr. Margaret Hamburg initiated another review of whether to keep Avandia on the market. As part of that review, FDA investigator Dr. Thomas Marciniak presented a devastating report on RECORD's shortcomings, detailing how the RECORD study minimized Avandia's heart risks: one death among the drug takers, for example, was missing



from the final tally, and discrepancies in some cardiovascular data favored Avandia by a ratio of 4 to 1. The congressional investigation also uncovered e-mails indicating that GSK executives had managed to persuade the trial's supposedly independent steering committee to publish interim results that demonstrated how inconclusive the heart risk was. The trial's design, Marciniak found, was "completely inappropriate and biased."

For its part, GSK insists the drug is indeed safe and says it has played fair with the data. It lists multiple studies that are inconclusive or show no increase in heart risk for Avandia. It says it has disciplined the sales representatives who triggered the FDA admonition; it updated its report on Avandia tests after the FDA's 2008 warning letter. "GSK continues to stand behind Avandia," says spokesman Kevin Colgan. "The facts will support our position." Using the most powerful argument of all, GSK says diabetics desperately want and need drugs to lower their blood-sugar levels. All of this persuaded the FDA advisory group this July to narrowly vote not to pull Avandia off the market, citing a lack of strong evidence that it should be withdrawn. Eleven years after the drug was approved, neither GSK nor the FDA could yet prove Avandia was safe.

GSK certainly had reason to dispel the uncertainty if it could. In 2001, it ran a calculation of what the "net sales downside" would be if the cardiovascular "safe-

ty issue intensifies" and found that for 2002-04, potential lost revenue amounted to \$600 million, according to the civil-court proceedings obtained by TIME. GSK reported a 10% drop in profits for the fourth quarter of 2007, partly as a consequence of a drop in Avandia sales following the publication of the Nissen article. Now GSK has other financial concerns. In March the company put aside \$3.5 billion for "legal and other disputes." In May it paid \$60 million to settle 700 Avandia civil cases; in July it reportedly offered to pay \$460 million to settle civil cases claiming the drug caused heart attacks. GSK declines to discuss the costs of—or anything else about—the investigation the FDA is undertaking against it.

That investigation may indicate that change is coming to the FDA. Government and independent watchdogs say the agency has made some progress. In 2009, government auditors found that the FDA had begun to bolster the role of drug-safety monitors. The Health and Human Services inspector general said last March that the FDA has boosted its prescription database of postmarket reports.

But none of that addresses the issue at the heart of the Avandia case. Science is often inconclusive, and the FDA rightly argues that surveys like Nissen's are sometimes wrong. Where the FDA fell down on Avandia was in allowing GSK to perpetuate the uncertainty about safety rather than clarify it. In 2007, the FDA gained new powers to require postmarket safety trials, but FDA leaders admit they're still learning how to use them. Grassley wants to give FDA safety monitors even more power, and former FDA chief Mark McClellan says the agency should use newly computerized medical records to track safety data in near real time.

But with the FDA ever more dependent on industry user fees, and with new drug-safety concerns emerging year after year, it will take more than faster data retrieval to restore the reputation of an agency that was once synonymous with trust in the public mind. The FDA will have to start forcing companies to be transparent and call them out on it when they're not. Says the medical reviewer Misbin: "Companies are always going to present their best face. It's our job to say no." In that sense, the FDA just needs to perform the task it was charged with more than 100 years ago: protecting the public interest by keeping industry honest. —WITH REPORTING BY SUSAN WEILL/NEW YORK