

St. Petersburg Times

DRUG'S CHILLING PATH TO MARKET

[SOUTH PINELLAS Edition]

St. Petersburg Times - St. Petersburg, Fla.
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Date: May 27, 2007
Section: NATIONAL
Text Word Count: 2591

Document Text

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How a broken FDA approved a cold antibiotic despite a wide trail of alarms.

Dr. Campbell got greedy.

The drugmaker was offering doctors \$400 per patient to test Ketek, its new antibiotic for persistent colds and coughs.

Anne Kirkman Campbell, a family practice doctor in Gadsden, Ala., signed up 400 patients, more than any other doctor in the country.

When one patient backed out, Campbell forged the consent form and faked the data. A company hired to oversee the study caught the doctor's forgery, along with unmistakable signs of fraud involving dozens of other patients, and alerted the drugmaker.

But the pharmaceutical company, which stood to make hundreds of millions of dollars on Ketek, didn't stop Campbell or report her crime to the Food and Drug Administration. Instead, it included her dubious data in its submission to the agency.

Even after federal regulators stumbled on Campbell's fraud and uncovered problems at several other study sites, the FDA approved Ketek.

A system of checks and balances had become one of winks and nods. Then people started dying of liver failure.

Aventis Pharmaceuticals Inc. thought it had a blockbuster in Ketek (pronounced kee-tek). It would be marketed as the next amoxicillin, a widely used antibiotic to treat the sinusitis and bronchitis that plague millions of Americans each year.

But before Ketek could come to market, the FDA required proof that the expensive new drug was at least as good as the existing treatment. So Aventis devised Study 3014, a clinical drug trial involving 1,800 private physicians and thousands of their patients nationwide.

As is common practice in the industry, Aventis opted to have a third party conduct the study. It paid PPD Inc., one of the world's biggest contract research organizations, some \$20-million for the work.

Ann Marie Cisneros had worked for PPD for three years when she was sent to check up on Campbell in early 2002. The doctor had recruited more than 1 percent of Gadsden's adult population for the Ketek study.

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Cisneros noticed that none of the doctor's staff would look her in the eye. Combing patient files, Cisneros found that the doctor had enrolled her entire staff and several family members in the study.

Patient consent forms had been signed every few minutes and at times when the office was closed. Medical records had been edited, with notations of "sinusitis" and "bronchitis" added so patients would qualify for the trial.

"It appeared the patient was coming into the office for one condition and the doctor was writing in something else later," Cisneros said. "That's how Dr. Campbell ended up with 407 people."

By comparison, another local doctor found only 12 patients who met the study criteria.

The Ketek study was demanding; it required that patients come in for three office visits and blood draws over five months. But not a single one of Campbell's patients had dropped out.

"That just doesn't happen, period," said Cisneros, noting that even small studies experience dropouts.

The doctor didn't appreciate the scrutiny. She told Cisneros that she wouldn't have enrolled so many patients had she known it would trigger an audit.

"That's just scary," Cisneros said. "Dr. Campbell didn't get away with it because she hadn't learned the system."

Certain she had found fraud, Cisneros called her manager at PPD. She also took the unusual step of contacting a consulting partner responsible for ensuring patient safety in clinical trials. Copernicus Group IRB, also paid by the drug company, had access to trial subjects' names and phone numbers. Monitors like Cisneros usually had limited identifying information.

"I wanted them to call some patients and see if they'd really agreed to be in the study," said Cisneros, who suspected patients were enrolled without their knowledge. "But the woman at Copernicus said, 'Let's see what Aventis does about this.'"

Spokeswomen for Copernicus and PPD declined to comment.

After Cisneros returned to PPD, she and her bosses had a teleconference with the drugmaker. She said her concerns about the doctor's conduct, including the likelihood that consent forms had been forged, were ignored.

"I walked away from that meeting very frustrated," Cisneros said. "I'd never seen a sponsor so lackadaisical about a site."

A spokeswoman said the Paris-based drugmaker, which has since become Sanofi-Aventis, knew of "deviations" at Campbell's site but didn't know they amounted to fraud until a subsequent FDA investigation.

"We were aware of issues at that site and had gone in to try to rectify them," said spokeswoman Lisa Kennedy. "We strongly object to any characterization of wrongful conduct by Aventis."

Cisneros, who left PPD for a higher-paying job at a competing company, assumed someone in a position of authority would alert the FDA about Campbell.

But the Ketek study continued uninterrupted. In July 2002, the drugmaker submitted the trial results to the FDA - including data from all 407 patients at Campbell's site.

Stunned as Cisneros was about how Sanofi-Aventis and its partners handled the Ketek study, Dr. David Ross, a safety reviewer at the FDA, was equally alarmed by his agency's response.

While the FDA's drug approval division reviewed the Ketek data, its inspectors were conducting routine audits of the biggest study sites. Their first stop was Campbell's office, where they found such flagrant violations that they immediately called in the agency's criminal division.

FDA investigators visited nine other high-enrolling sites and discovered serious problems at every one. One doctor, whose medical license was on probation at the time of the study, was arrested for cocaine and gun possession soon after. FDA agents referred Campbell and three other doctors for criminal investigation and recommended expanding the inspections to additional sites.

But even as the FDA's Office of Criminal Investigation uncovered widespread problems, the agency's drug approval division proceeded to review the Ketek data.

In addition to its internal review, the FDA often has an outside, advisory group of experts evaluate trial data and recommend whether a drug should be approved. Ross, the FDA scientist, said he expected the Ketek advisory group would be told of concerns about the data's validity in light of the ongoing criminal investigations. He said he was appalled when his boss, Dr. Mark Goldberger, told him not to raise the issue with the outside experts.

"In general, I don't believe spending time on (data integrity) issues in front of the AC (Advisory Committee) will be productive," Goldberger wrote in an e-mail a few days before the January 2003 meeting.

The FDA recently said that at the time of the advisory meeting it had only preliminary information on problems with the Ketek study and wished to avoid "compromising the ongoing investigations."

But Ross said his bosses had plenty of options. "They could have told the committee what they knew in closed session. Or they could have postponed the meeting," he said. "I felt like I was being told to hide things."

The FDA's advisory committee recommended approving Ketek. After delaying its decision to get anecdotal information on Ketek's safety record overseas, the FDA approved the drug on April 1, 2004.

Less than a year later, the agency was notified of the case of Ramiro Obrajero Pulquero, a young Mexican construction worker in Charlotte. He had gone to his doctor with a cold and was prescribed Ketek. Three weeks later he was dead of liver failure.

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Acting on information provided by the FDA's criminal investigators, the U.S. Attorney's Office in Birmingham indicted Dr. Campbell on 21 counts of fraud. She pleaded guilty to one count of mail fraud and was sentenced to 57 months in prison.

In a phone interview from the federal prison in Lexington, Ky., Campbell admitted that she forged a consent form but declined to discuss other allegations of wrongdoing. Instead, Campbell, now 49, blamed the drug manufacturer for fast-tracking the trial.

"They seemed to want to rush you through everything," said Campbell, who had performed a half-dozen clinical trials for other drugmakers. "They didn't care how you did it. They wanted the trial over so they could get the data to the FDA."

Despite Campbell's "deviations" during the Ketek trial, once it was over Aventis hired her for a second study that spring. The drugmaker also flew Campbell to a conference in San Diego that summer so she could learn how to market Ketek to other physicians.

In the fall of 2002, when the FDA called to schedule a routine audit, Campbell said, Aventis told her to delay the agent for a week.

"Then they flew in two doctors to prep me and four to six girls to go through my files," said Campbell, who said the drug company's representatives suggested appropriate responses to the FDA's queries.

Sanofi-Aventis' spokeswoman said it is normal for a drug company to help a doctor prepare for a site inspection. She said Campbell was advised to answer the FDA's questions truthfully. The drugmaker ended its relationship with the doctor after the FDA initiated its criminal investigation, she added.

Campbell said she was amazed when the court said the drugmaker was a victim of her fraud and ordered her to pay \$925,000 restitution. In a court filing last year, Campbell appealed the restitution order.

Aventis "had been made aware of the fraud at my site by PPD," she argued. "At NO TIME did they (Aventis) attempt to

stop my participation."

Late last month, Campbell's motion was denied.

Ketek is the latest in a string of drug debacles that have tarnished the FDA. Testifying with Ross and Cisneros at a congressional hearing in February, a veteran FDA epidemiologist put the drug's history into perspective.

"The Ketek story is about the FDA's betrayal of the public trust," said Dr. David Graham, who has been with the agency for 23 years. "Unfortunately, Ketek is not an anomaly."

Safety recalls of medicines are occurring at twice the rate this decade as in the 1990s, with the 2004 withdrawal of Merck's Vioxx the best-known example. Also on the rise: relabeling drugs to include deadly side effects.

Ross, the FDA safety reviewer, ended a 10-year career with the agency in November and now is an assistant clinical professor of medicine at George Washington University in Washington, D.C. He said the agency's growing reliance on industry dollars has fostered a "culture of approval."

Last year drugmakers paid the FDA more than \$300-million in user fees, accounting for more than half of the agency's drug review budget.

"Even if a product doesn't work or we don't know how it works, there is pressure on managers that gets transmitted down to reviewers to find some way of approving it," Ross said. "There's been a cultural shift at the FDA, and the pharmaceutical industry is now viewed as the client."

Ross, an infectious disease specialist, stressed that Ketek was being marketed for common ailments that often get better over time without the use of antibiotics. "This was not a drug that anybody thought was necessary in terms of public health. But it was important for the company financially."

Cisneros, who continues to work as a clinical trial monitor, is waiting for someone other than Campbell to be held accountable for how the Ketek study was mishandled.

"We're all just afraid nothing will come of this," she said. "But the system is going to spiral out of control. It's already teetering."

In mid December, an FDA advisory committee discussed the growing evidence linking Ketek to liver failure: 53 reported cases, including two people who needed liver transplants and five deaths.

Among them was Obrajero, who left behind two young daughters. His widow, distraught that a 26-year-old who rode motorbikes and played soccer could be killed by a cold, sought out a lawyer. She was unaware that his case, along with two other Ketek-related liver injuries treated within a few months at the same hospital, had been reported to the FDA and written up for a medical journal.

The lawyer, Neal Rodgers of Charlotte, said he thought he had a routine medical malpractice case until his researcher stumbled on the article in the *Annals of Internal Medicine*.

"She said, 'You won't believe it. This guy's autopsy is all over the Internet,'" said Rodgers, who sued Sanofi-Aventis, PPD, Campbell and three other doctors involved in Study 3014.

Dr. William Lee, an FDA consultant and advisory committee member, said only 10 percent to 12 percent of drug-related adverse events are reported, so the full impact of Ketek may never be known.

"But the drug probably should not be used as a daily antibiotic, which is how they'd love to market it," said Lee, director of the Clinical Center for Liver Diseases at the University of Texas Southwestern Medical Center in Dallas.

On Feb. 12, the day before the congressional hearing on Ketek, the FDA sharply curbed the drug's use. With health risks outweighing the benefits of using the drug for common colds, the agency limited Ketek's use to treatment of

community-acquired pneumonia.

Until then, Ketek had been one of the most successful antibiotic launches in history, bringing Sanofi-Aventis nearly \$400-million in U.S. sales.

Since the FDA restricted its use, Ketek sales have dropped by half.

Times researcher Carolyn Edds contributed to this report. Kris Hundley can be reached at hundley@sptimes.com or (727) 892-2996.

BY THE NUMBERS

1.56 Percent of newly approved drugs pulled from market, 1989- 1991

5.34 Percent of newly approved drugs pulled from market, 1997- 2000

10 Number of complaints to the FDA about clinical drug trial irregularities in 1998

350 Number of complaints to the FDA about clinical drug trial irregularities in 2006

22 Number of drugs approved by the FDA in 2006

6 months Average FDA review time for priority drugs in 2006

21 months Average FDA review time for priority drugs in 1993*

10 months Average FDA review time for standard drugs in 2006

27 months Average FDA review time for standard drugs in '93*

* First full year in which the pharmaceutical industry paid user fees to the FDA in return for speedier drug approvals. Sources: FDA, U.S. Government Accountability Office

About Ketek

Use: Originally approved for acute sinusitis and chronic bronchitis as well as community-acquired pneumonia. In February, the FDA limited its use to pneumonia.

Manufacturer: Sanofi-Aventis, Paris.

Type of drug: Antibiotic (telithromycin).

FDA approval: April 1, 2004.

Potential side effects: Liver injury, loss of consciousness, visual disturbances; not to be taken by people with myasthenia gravis (a muscle disease).

U.S. sales through 2006: \$374-million.

U.S. prescriptions through 2006: 6.1-million.

Estimated loss due to restrictions on use: \$575-million.

Sources: U.S. Food and Drug Administration, IMS Health, Sanofi- Aventis

[Illustration]

Caption: PHOTO, SARA D. DAVIS - Special to the Times: The whistleblower: Ann Marie Cisneros Though she reported

fraud, nobody acted on it. She says drugmakers know that the FDA is understaffed and unlikely to catch problems in clinical drug trials. PHOTO, JAY L. CLENDENIN - Special to the Times: The safety expert: Dr. David Ross The FDA approved Ketek even though he urged the agency to wait because of fraud at several study sites. He says Ketek and recent food safety issues show that the FDA needs additional funding and a change in its culture. PHOTO, Special to the Times: The fraudulent doctor: Anne Kirkman Campbell She says the drugmaker was well aware of serious problems with the Ketek study - but she's the only one who has paid the price. "It seemed like I was the scapegoat for the whole thing." PHOTO, EDMUND FOUNTAIN - Times: About Ketek

Credit: Times Staff Writer

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Abstract (Document Summary)

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