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REPORT

An Inside Look at the FDA's Sordid Drug Approval Process

Some people still think the FDA protects the public against dangerous drugs.

Too often, however, the FDA works hand-in-hand with pharmaceutical companies to allow questionable drugs on to the American marketplace.

The following re-print from the Los Angeles Times provides an inside look at how a large drug company conspired with high-level FDA officials to sell a lethal drug to Americans.

FDA-approved drugs kill over 125,000 Americans every year. This Los Angeles Times exposé reveals how dangerous drugs make it through a regulatory process that is supposed to put safety first.



Risk Was Known as FDA OK'd Fatal Drug

By: David Willman LA Times staff writer

Study: New documents show Warner-Lambert trivialized liver toxicity of diabetes pill Rezulin while seeking federal approval. Inside help from senior regulators is trumpeted in company memos.

Executives of the Warner-Lambert Co. brimmed with confidence as they marched the now-discredited diabetes pill Rezulin toward government approval in the mid-1990s. And with good reason, according to newly obtained company and government documents.

As portrayed in the records, officials of the Food and Drug Administration provided Warner-Lambert with inside information and favors at critical moments throughout the development and marketing of Rezulin. At least one senior manager believed that if an FDA medical officer who had questioned the drug's safety and effectiveness didn't please the company, he would be "out." Soon enough, he was, prompting another executive to report internally that a "hurdle" had been cleared for Rezulin.

The records also shed new light on the state of knowledge within Warner-Lambert of Rezulin's potential danger: Executives knew that patients who took the drug in clinical studies had suffered life-threatening liver damage—yet the company assured an FDA panel that the risk was trivial.

The company's assurances helped win swift approval for Rezulin four years ago from the FDA. The drug was withdrawn in March of last year after being cited as the suspect in 391 deaths, including 63 that involved liver failure. Rezulin generated sales of \$2.1 billion.

Opening a regulatory door

The new documents, which have been kept from public view by court orders or by the FDA, were obtained by The Los Angeles Times. The internal memos and e-mails provide an intimate view of how a company seeking a blockbuster drug collaborated closely with the public health agency responsible for ensuring that medicines are proved safe and effective.

The FDA's collaborative role with Warner-Lambert began at the same time that the agency was being urged by Congress and the White House to function less as an adversary and more as a "partner" of the \$100-billion pharmaceutical industry.

This transformation of the FDA, first evident in the streamlined approvals of experimental AIDS drugs, opened a regulatory door. Pharmaceutical companies pushed for similarly rapid consideration of a wide range of remedies, regardless of whether the products offered lifesaving benefits.

In Rezulin, the FDA was faced with a drug that had not been proved to save lives or to reduce the serious complications of adult-

onset diabetes.

It was against this backdrop that Warner-Lambert's vice president for diabetes research, Dr. Randall W. Whitcomb, told an FDA advisory committee on Dec. 11, 1996, that occurrences of liver injury among Rezulin patients were "comparable to placebo" in the clinical studies. In fact, the incidence among patients who took the drug was well over three times higher than for those given placebo pills.

Among those patients who took Rezulin, 2.2% experienced liver injury, compared with 0.6% for those who took the placebo.

In a recent sworn deposition for lawsuits brought by plaintiffs from Texas, Missouri and West Virginia, Whitcomb defended his earlier characterizations.

"Comparable' is, is, you know, is an interesting word," Whitcomb testified. "Is 2.2% different than 0.6%? ...I think you could look at 2.2 and 0.6 and say that those are similar numbers, you know, when you look at this now. I mean, 'similar' is a—is a very broad term. ...I don't think that these numbers are, are all that different."

Liver monitoring label is abandoned

But the newly obtained documents reveal that concern about liver toxicity within Warner-Lambert was such that the company prepared a label for the drug in 1996 recommending that patients "should be monitored at three months then every six months."

The company abandoned the recommendation for liver monitoring before seeking the FDA advisory committee's endorsement in December 1996. Such a condition would have drastically reduced Rezulin's sales potential, according to doctors who point out that at least nine other less-risky diabetes drugs were available.

Warner-Lambert did not publicly recommend liver monitoring for Rezulin patients until late October 1997—and then only after the first reported liver-failure deaths among those who were prescribed the drug.

Warner-Lambert executives have said in the past that they did not see the need earlier for monitoring because no patient suffered liver failure in the original clinical studies.

Whitcomb, 46, who was Warner-Lambert's chief medical proponent of Rezulin from 1993 to 2000, is now a part-time consultant to Pfizer Inc., which acquired Warner-Lambert in a merger last year. A Pfizer spokesman, Bob Fauteux, said the company had no comment in response to questions posed about Whitcomb's conduct. Whitcomb did not return a phone call placed to his home.

In recent sworn testimony, Whitcomb said that he and others at the company "did not believe monitoring was necessary at the time the product was launched."

However, at least 12 Rezulin patients in the studies were found to have potentially life-threatening liver toxicity, the records show. All of the patients had markers of liver toxicity 10 to 30 times over the "upper limit of normal."

On June 30, 1993, a company memo described the earliest case, a 63-year-old man who experienced "abrupt elevation" of liver enzymes after taking 400-milligram doses daily for five weeks. The man was taken off Rezulin—but the damage to his liver persisted, according to the memo.

Records also show that before the drug was approved on Jan. 29, 1997, at least four Rezulin patients in clinical studies were known by the company or its consultants to have suffered jaundice, a complication that carries a 10% fatality rate. No instances of jaundice or other signs of life-threatening liver toxicity occurred among the placebo patients.

On June 29, 1995, Whitcomb informed company-paid physicians testing Rezulin in the U.S. that a patient in Japan was hospitalized with jaundice after taking the drug for three months. "The Japanese investigator believed this hepatic dysfunction is probably related to [Rezulin]," Whitcomb wrote. But he concluded that, in Warner-Lambert's opinion, "causality is indeterminable."

In December 1996, Whitcomb assured the FDA's Endocrine and Metabolic Drugs Advisory Committee that Warner-Lambert had gathered results from clinical studies worldwide, yet he cited only one case of jaundice occurring among Rezulin patients.

"We also have all of the safety data from 629 patients from Europe," Whitcomb said. "And we have another 1,000 patients from Japan.... We have all of the safety data available from that."

Belated public disclosure

It was not until March 26, 1998—nearly six months after the first liver-failure deaths—that Whitcomb publicly acknowledged the severe liver-toxicity cases observed in clinical studies. Whitcomb did so not in a mass-mailed letter to physicians but in a seven-

paragraph letter published by the New England Journal of Medicine.

This belated disclosure seemed to surprise Warner-Lambert's Japanese partner, Sankyo Co. On March 31, 1998, a Sankyo executive wrote to a Warner-Lambert vice president, asking why the "extreme" cases described by Whitcomb were not reported to the company and Japanese authorities on a "timely" basis.

Two months later, a consultant hired by Warner-Lambert to prepare an inventory of liver injury among patients who were prescribed Rezulin complained that the company had understated the number of deaths. The inventory was to be submitted to the FDA by Warner-Lambert's Parke-Davis drug unit.

"We have serious concerns about the case files generated for us by Parke-Davis," consultant Linda Miwa of the Degge Group Ltd. of Arlington, Va., wrote on May 5, 1998, to a Warner-Lambert vice president. "For example, the table of events lists five deaths. By our assessment, there are 14 liver deaths alone. We feel something is truly amiss here."

The documents show that more mistrust followed the liver failure and death, on May 17, 1998, of an East St. Louis, Ill., high school teacher who had taken Rezulin in a diabetes-prevention study sponsored by Warner-Lambert and the National Institutes of Health.

While the death prompted NIH officials to banish Rezulin from the ongoing study, an FDA medical officer, Dr. Robert I. Misbin, told a colleague in a July 22, 1998, e-mail: "Parke-Davis is clearly unwilling to inform physicians about the grossly elevated liver enzymes which occurred [sic] during the clinical trials. This is not surprising [sic] because they did not inform the Advisory Committee either." Misbin had asked the company to acknowledge the cases in a "Dear Doctor" letter to physicians nationwide.

A consultant to Warner-Lambert who helped conduct two of its studies alleged one year ago in a letter to Sen. Edward M. Kennedy (D-Mass.) that the company "deliberately omitted reports of liver toxicity and misrepresented serious adverse events experienced by patients in their clinical studies." One of the cases involved a patient who was hospitalized with jaundice. The company denied the accusations, made by Dr. Janet B. McGill, a St. Louis endocrinologist.

A well-crafted partnership

The new documents reveal that, throughout Rezulin's rise and fall, senior FDA officials quietly collaborated with Warner-Lambert. Those who provided behind-the-scenes help to the company included Dr. Murray M. "Mac" Lumpkin, who now is among those being considered for appointment as FDA commissioner, and Dr. Henry G. Bone III of Detroit, chairman of the FDA advisory committee.

One of the company's earliest concerns was the role of Dr. John L. Gueriguian, the FDA medical officer assigned in the early 1990s to examine Rezulin and its chemical class of drugs. Gueriguian, the newly obtained records show, voiced concern to Warner-Lambert as early as January 1994 about Rezulin's "potential toxicities."

The next year, Gueriguian challenged whether Warner-Lambert's proposed design for studying Rezulin in a forthcoming clinical trial would provide a legitimate evaluation of the drug's usefulness. On Aug. 7, 1995, the day before FDA officials were to meet internally to resolve the matter, Gueriguian's boss, Dr. G. Alexander Fleming, phoned a senior manager at Warner-Lambert, Mary E. Taylor.

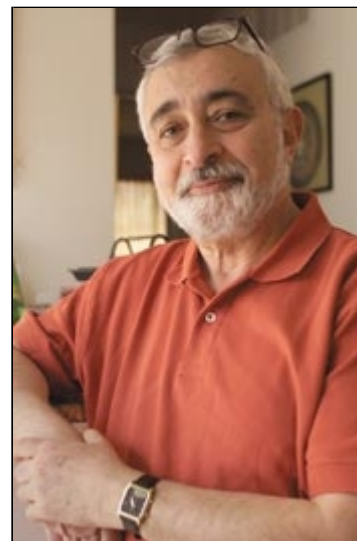
FDA officer is cast out

According to Taylor's memorandum, "Dr. Fleming asked me to call Dr. Gueriguian.... He also offered that if our discussion did not go well, he would ease Dr. Gueriguian out." Taylor distributed this memo to six company executives.

One of those executives had written in a company e-mail on June 22, 1994, that he and Fleming had just discussed the company's "interactions" with Gueriguian. According to the e-mail, Fleming "implied that, while Dr. Gueriguian will remain for now the [medical] reviewer," he would "likely" be replaced.

Fleming said this week that he did not recall making a "commitment" to Taylor to remove Gueriguian from the review of Rezulin if she became displeased.

After Warner-Lambert complained in October 1996 that Gueriguian used a profanity to describe Rezulin, the FDA stripped him of any further role with the drug. According to Gueriguian, he told Taylor, "You can't shine shit with words." By that time, the veteran medical officer was recommending rejection of the pill—warning in a written review of its potential to harm the liver and the heart. He also questioned its worthiness as a blood-sugar-lowering agent.



Dr. John L. Gueriguian, records show, voiced concern to Warner-Lambert as early as January 1994 about Rezulin's "potential toxicities."

Photo: Chuck Kennedy, for the Times

The FDA's banishment of Gueriguian clearly pleased Warner-Lambert's executive vice president for regulatory affairs, Irwin G. Martin, who e-mailed colleagues on Oct. 16, 1996, saying, "We're over the JG hurdle." Martin wrote that Fleming assured him, "John [Gueriguian] is 'out of the picture.' His review is complete.... It will not go to the advisory committee."

Gueriguian was formally removed from the review of Rezulin on Nov. 4, 1996.

On Dec. 2, 1996—nine days before the FDA advisory committee would meet to consider Rezulin's approval—Fleming e-mailed to Martin an encrypted copy of Gueriguian's medical review. That same day, Fleming wrote in a separate e-mail to colleagues that Lumpkin had told him Gueriguian's review "is not FOIable." By this, Fleming suggested the document would be withheld from public view because consumers, the news media or others could not obtain it under the Freedom of Information Act.

The FDA staff withheld the existence of Gueriguian's review from members of the advisory committee. Lumpkin, at the time the No. 2 official of the agency's drug review center, did not return calls last week.

On Dec. 9, 1996, two days before the advisory committee meeting, Fleming e-mailed Martin: "The drug looks like it ought to be on the market. Loosen up and put on a good presentation. Call if you need help."

Senior agency officials remained helpful as the company pushed to keep Rezulin on the U.S. market in the face of the ever-mounting liver failures and deaths and the withdrawal of the product from Britain.

On June 6, 1998, just days after the NIH banished Rezulin from its study, Martin wrote in a company memo that he had discussed "the current Rezulin issues" with Lumpkin while the two attended a drug-industry trade group gathering. According to Martin's memo, a subordinate of Lumpkin, Dr. James Bilstad, at that time was considering a change in Rezulin's labeling that could have dealt a crippling blow to the drug: A recommendation for twice-a-month liver testing for all patients.

Rezulin's safety assured, despite the facts

Publicly, the company and the FDA were still assuring doctors that the risk of liver failure was very rare and could be managed with once-a-month monitoring for the first half-year of use. Martin wrote that he and Lumpkin "discussed alternatives" to the imposition of twice-monthly monitoring.

"He [Lumpkin] also agreed that we need to evaluate these [liver-failure] cases, and not simply act because NIH did." The FDA abandoned the idea of recommending twice-monthly monitoring and continued to assure doctors that Rezulin could be used safely.



In the same memo, Martin said that he expressed "concern" to Lumpkin about the FDA's Misbin. The previous month, Misbin was instructed by his bosses to cancel his commitment to discuss Rezulin and its liver toxicity at a public conference in the Washington area.

"I thanked Mac for his help on the last issue with Misbin wanting to speak publicly about Rezulin hepatotox," Martin wrote, adding in a subsequent e-mail that Misbin's appearance was "canceled by Mac."

Lumpkin also encouraged Warner-Lambert to more forcefully highlight anecdotes of happy Rezulin patients, wrote Martin in his June 6, 1998, e-mail. "Mac suggested those stories need to come out."

Another crucial moment for Warner-Lambert came in spring 1999, when the FDA convened the endocrine drugs advisory committee to reassess Rezulin. Despite a damning presentation of the drug's danger by an agency epidemiologist, the committee voted unanimously that Rezulin should remain on the market.

With the drug's status still in limbo at FDA headquarters, Martin recalled conferring "privately for about one hour" with committee chairman Bone regarding strategy for persuading the agency staff to follow the committee's recommendation. The meeting occurred in Detroit.

"He [Bone] thought we should be very pleased with the outcome of last month's meeting; realistically, we could not have done better," Martin wrote on April 24, 1999. ".There were and are many in the agency who feel that Rezulin should have been removed." (Bone participated with a conflict-of-interest "waiver" from the FDA; he has declined to identify the circumstances that prompted issuance of the waiver.) Bone did not return calls seeking his comment for this article.

Martin also wrote that Bone, whose advisory committee is supposed to be impartial and makes recommendations on a range of diabetes drugs, advised Warner-Lambert to "focus our competitive efforts on comparative safety issues—the other products have clearly given us openings."

Martin's description of his meeting with Bone elicited this e-mail response two days later from a Warner-Lambert sales executive, J. Wright Witcher: "Congratulations Irwin, on what sounds like an unusually fruitful discussion... this is helpful to us."

Pfizer, in a financial statement last fall to the Securities and Exchange Commission, said that as of mid-October it was defending against 383 Rezulin-related lawsuits filed in state and federal courts.

In addition to the civil suits, prosecutors in the U.S. attorney's office in Greenbelt, Md., began questioning FDA officials last year about circumstances surrounding the approval of Rezulin.

Times researcher Janet Lundblad in Los Angeles contributed to this story.

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