REZULIN:
Fast-Track Approval and a Slow Withdrawal

■ Diabetes drug stayed on the market a year after being listed among the most risky.

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Soon after Warner-Lambert Co. submitted the diabetes drug Rezulin for FDA review in the summer of 1996, the medical officer assigned to examine it began finding problems. Dr. John L. Gueriguian cited Rezulin's potential to harm the liver and the heart. He questioned its viability in lowering blood sugar for patients with adult-onset diabetes.

Gueriguian was stripped of the assignment in November 1996 after Warner-Lambert complained that he used intemperate language while discussing the drug. His medical review--recommending against approving Rezulin--was purged from agency files and withheld from an FDA advisory committee.

Officials completed the review of Rezulin within six months and approved it in January 1997. Warner-Lambert's chief executive told investors he foresaw a "billion-dollar blockbuster."

By fall 1997, dozens of patients on Rezulin had been hospitalized and a handful of cases of sudden liver failure had been reported to the FDA.

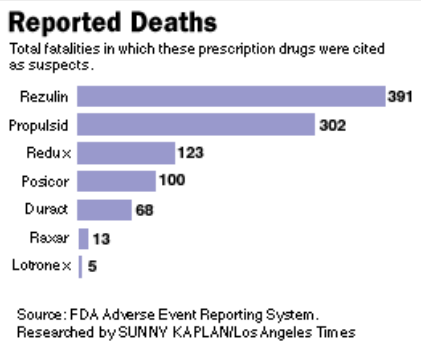
Those first cases prompted the removal of Rezulin from the market in Britain on Dec. 1, 1997--sparking an 18% drop in Warner-Lambert's stock on the New York Stock Exchange. But senior FDA officials stood behind Rezulin by embracing a series of incremental labeling changes.

Two changes came in late 1997 and a third came in July 1998. Each change recommended the monitoring of patients' liver functions as a means of safeguarding against organ failure.

In March 1999, a senior FDA epidemiologist, Dr. David J. Graham, warned that Rezulin was among the most dangerous drugs on the American market. He said that patient monitoring would not protect them from liver failure. Indeed, three patients who were monitored monthly in controlled studies, including one by the National Institutes of Health, suffered liver failure and died.

"The death of the patient . . . in [the] NIH study in May 1998 provided strong evidence that Rezulin could not be used safely," Dr. Robert I. Misbin, an FDA medical officer, wrote in a July 3, 2000,

letter to the House Energy and Commerce Committee.



Rezulin had not been proved to save lives or to reduce the serious complications of adult-onset diabetes. A fourth label change was implemented in June 1999. But deaths and hospitalizations continued.

The FDA announced on March 21 that Rezulin would be pulled from the market. By that time, the agency had tied 63 liver failure deaths to the drug. Reports filed with the agency through June 30 cited Rezulin as a suspect in a total of 391 deaths.

Officials have never estimated how many Rezulin patients died of heart-related complications. As a condition of approval, the FDA had requested that Warner-Lambert perform a study of the drug's effect in heart-failure patients; the study was never completed.

Before and after the withdrawal, FDA officials overstated Rezulin's scientifically proved benefits. For instance, agency ombudsman James Morrison wrote in June that Rezulin "has been shown to reduce or delay long-term, serious effects of diabetes, including death." Asked the basis for this claim, FDA spokesman Laurence Bachorik said the comments "were not intended as definitive scientific observations."

Six specialists who were involved in Rezulin's approval recently questioned why the drug was given a fast-track review. A "Lessons Learned" report posted in November on the agency's Web site said: "A final major concern of the subjects interviewed . . . was the lack of adequate time to review the application."

Woodcock said agency specialists had hoped Rezulin would offer "significant improvement" over the nine or more existing treatments for adult-onset diabetes. As for the decisions that kept Rezulin on the market, Woodcock said she wanted first to see if two newer drugs approved in 1999 were less toxic to the liver. Gueriguian said Rezulin is an example of how senior FDA officials relied on a company's hopes at the expense of public health.

"It really doesn't matter if it was incompetence or dishonesty," he said. "The result is the same: People died unnecessarily."

Rezulin generated sales totaling $2.1 billion for Warner-Lambert in its three years on the U.S. market.

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