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## REPORT

### The Rise and Fall of the Killer Drug Rezulin

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by David Willman

The suffering persisted for more than two years. Initially, there were four known victims. Then 21. Then 33. Finally, 63 confirmed fatalities.

All the while, federal authorities watched, waited and hoped the deaths would stop.

It was not until a disparate collection of physicians inside the U.S. Food and Drug Administration waged a remarkable revolt that the agency was forced to reverse course. These specialists—dubbed the “Termites” by one medical officer—combined meticulous research and bluntly worded e-mail messages to upbraid their government superiors for contributing to the needless deaths of patients.

How the Termites prevailed in toppling Rezulin, a blockbuster diabetes drug that generated \$2.1 billion in sales, illuminates one of the most important reversals in FDA history.

A reconstruction of Rezulin’s rise and fall shows that senior government officials repeatedly played down the drug’s propensity to cause liver failure and death. Before it was withdrawn on March 21, the FDA assured doctors and patients that Rezulin’s potential benefits in lowering blood-sugar levels outweighed its grave risks.

Diary entries, internal correspondence and interviews with participants reveal the pivotal roles of separate factions inside the FDA: the Termites, spearheaded by the efforts of Dr. David J. Graham, and the agency’s most senior officials, led by Dr. Murray M. “Mac” Lumpkin.

As deputy director of the FDA’s drug-evaluation center, Lumpkin helped make Rezulin the nation’s fastest-approved diabetes pill and, to the end, resisted its withdrawal.

Lumpkin said that he had no misgivings about keeping Rezulin on the market for so long. The drug finally was pulled, Lumpkin said, only when it became “outmoded” in comparison to newer pills for adult-onset diabetes.

After listening to Lumpkin defend the handling of Rezulin on May 19 at an FDA advisory committee meeting, one panelist, Dr. Jules Hirsch of Rockefeller University, shook his head.

“I don’t share the point of view of a wonderfully happy outcome, of how well the system has worked,” Hirsch said. “Because a lot of people died of this thing. And a lot more people than we know died.”

Indeed, the FDA’s sustained support of Rezulin had consequences: 63 confirmed deaths from liver failure and thousands of liver injuries. Because adverse events from prescription drugs are reported voluntarily, typically by doctors and hospitals, Rezulin’s estimated toll is perhaps 10 times higher, experts say.

As the deaths kept escalating, the FDA responded by recommending multiple regimens of blood testing, called “monitoring,” as a means of safeguarding patients from liver failure. From the fall of 1997 through mid-1999, the FDA and the manufacturer, Warner-Lambert Co. of New Jersey, agreed to four liver-monitoring recommendations.

Yet no scientific proof existed then, or now, that monitoring would protect Rezulin patients, according to the FDA’s own research and interviews with physicians.

“It was a hope,” said Dr. Srini R. Vasa, a liver specialist based in Kansas City, Mo., who treated three Rezulin patients with liver failure, two of whom died. “There were a lot of lives lost and a lot of lives changed. . . . It did not make the drug safer.”

The FDA has overseen withdrawals of nine prescription drugs since fall 1997, an unprecedented number within such a short span. However, of those nine, the agency granted “fast-track” approval to only one: the oval, tan pill marketed as a diabetes breakthrough.

Rezulin thus becomes a touchstone for federal policymakers and for the doctors, patients and family members so directly affected by the government’s decisions.

This chronology of the struggle over Rezulin is based on previously undisclosed documents and scores of interviews conducted over the last three years with government and private physicians.

Doctor learns of liver failure deaths

Anxiety washed over him in a flash.

It was a Friday afternoon in early October 1997 and Dr. Robert I. Misbin had just

FDA Senior Officials  
FDA decision-makers who kept  
Rezulin on the market despite scores  
of confirmed liver failure deaths:

gotten vexing news from two Warner-Lambert executives: Patients taking Rezulin were beginning to die of liver failure.

When he hung up the phone at his government desk, Misbin felt a singular anguish. As an FDA diabetes specialist who advocated the approval of Rezulin, he had failed to confront the danger posed by the drug.

After relaying word to his supervisor, Misbin was alone with a central question:

How could this have happened?

Standing 5 feet, 11 inches, with prominent cheekbones, a graying beard and dark

Dr. Jane E. Henney  
53, the commissioner of the FDA,  
ordered a reassessment of Rezulin in  
January 1999 following disclosures in  
The Times concerning the agency's  
handling of the drug. Unlike her  
predecessor, Dr. David A. Kessler,  
Henney has maintained a low profile  
on the national stage.

features, Misbin is not easily pigeonholed. His mien at first impression is one of unflinching seriousness.

Next to an affinity for opera (he attends regularly and keeps a black-and-white picture of the late soprano Maria Callas framed in his living room), Misbin's passion is medical ethics. He has fundamental concerns about how patients are treated in clinical trials.

After graduating from Boston University Medical School, Misbin in 1976 arrived at Ceiba-Geigy, a drug company that then was defending its own lethal diabetes pill,

Dr. Murray M. "Mac" Lumpkin 46, deputy director of the FDA's drug evaluation center, managed the "fast-track" approval of Rezulin. Lumpkin sided with the manufacturer of Rezulin in keeping the drug on the market for more than 29 months after the first reported liver failures and deaths.

called Phenformin.

Misbin, now 53, said that he found himself unable to accept the company's basic defense of Phenformin: Patients were dying because of preexisting complications or other factors, but not because of the drug itself.

In July 1977, the government declared Phenformin an "imminent hazard" and ordered its immediate banishment. Two decades later, Misbin would have feelings of *deja vu* about another flawed diabetes drug.

Firm seeks to make drug a 'Blockbuster'

By May 15, 1995, Misbin's first day as an FDA medical officer, Warner-Lambert was moving to position Rezulin for heavy sales. The company, a conglomerate that makes products ranging from Chiclets chewing gum to Listerine mouthwash, launched a multitiered strategy for transforming Rezulin into a "billion-dollar blockbuster."

Early slide-show pitches were made to Wall Street analysts, emphasizing the market of America's 15 million adult-onset diabetics and touting Rezulin's "new mechanism of action."

Warner-Lambert and its affiliates paid speaking or other fees to more than 300 doctors, from endocrinologists to family practitioners. The company flew diabetes specialists to the 1996 Olympic Games in Atlanta and provided accommodations at the Chateau Elan Winery and Resort.

Warner-Lambert also put on its payroll the government's top diabetes researcher, Dr. Richard C. Eastman, who at the same time oversaw the selection of Rezulin for use in a National Institutes of Health clinical trial.

Much of the excitement surrounding the emergence of Rezulin stemmed from its status as the first of a new class of drugs for treating adult-onset diabetes. Rezulin promised to lower blood sugar much the same as Glucophage, the market's top-selling diabetes pill, by helping the body better use its own insulin. Most of the eight other diabetes pills worked by stimulating the pancreas to secrete more insulin.

Patients with adult-onset, or Type 2, diabetes do not produce enough of their own insulin at the right moments or their bodies do not make efficient use of this hormone, which regulates the metabolism of blood sugar. Type 2 diabetes also can be treated effectively with changes in diet and exercise. The disease is distinguished from juvenile-onset, Type 1, diabetes, in which patients cannot produce their own insulin and would die without daily injections or infusions.

Soon after Warner-Lambert submitted its new-drug application for Rezulin in July 1996, the FDA for the first time in its history granted a six-month fast-track review to a diabetes pill. The FDA then was taking a year or more to examine standard new-drug applications.

The assignment of vetting Rezulin's safety and effectiveness initially fell to Dr. John L. Gueriguian, a veteran FDA medical officer. Gueriguian "emphasized that [Rezulin] offered very little significant therapeutic advantage" over existing diabetes medications, according to a summary of an FDA staff meeting on Aug. 22, 1996.

By the fall of 1996, Gueriguian concluded that Rezulin was unfit for approval and warned of its potential to harm both the liver and the heart. But Gueriguian came under fire from Warner-Lambert executives, who contacted the FDA's Lumpkin to complain about Gueriguian's use of intemperate language.

Effective Nov. 4, 1996, Lumpkin ordered Gueriguian removed from the evaluation of Rezulin and any further dealings with Warner-Lambert, according to physicians familiar with the matter. Gueriguian's medical review also was purged from agency files.

These actions sent an early and enduring message within the FDA: Challenging Rezulin was not without risk to one's career.

More study brings unsettling conclusion

"We have real trouble."

With this entry in his personal diary in October 1997, Misbin described

Dr. Janet Woodcock 51, director of the FDA's drug evaluation center, distanced herself from Dr. David J. Graham's findings in March 1999 and insisted that the benefits of Rezulin outweighed its risks. Woodcock, who has led the FDA's shift to faster drug approvals and less-adversarial relations with industry, sought withdrawal of Rezulin on March 21.

Sources: FDA records, "Who's Who in America," interviews. Compiled by David Willman and Janet Lundblad, Los Angeles Times.

The Termites  
A collection of about a dozen FDA specialists whose revolt helped topple Rezulin. Among them:

prophetically the darkening turn of events.

He recalls being startled the afternoon of Friday, Oct. 10, when the two Warner-Lambert executives informed him of the first liver failures.

Before recommending a regulatory response, Misbin studied Warner-Lambert's original research and the recent cases of liver damage. He reached an unsettling conclusion.

"We knew the essential truth - that Rezulin could cause liver failure," Misbin recalled. "There was a potential for a disaster."

The FDA is obligated under federal law to ensure that new and existing prescription

Dr. John L. Gueriguian  
64, opposed approval of Rezulin. [In  
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drugs are safe and effective for their intended use. The agency's quandary of what to do about Rezulin, medical experts say, was framed by this reality.

Compared to the constant risk of liver failure, patients would need to take Rezulin for years to gain potential benefits that could lessen the serious complications of diabetes, such as blindness or amputation. And Rezulin was one of 10 pills available to lower blood-sugar levels for adult-onset diabetics.

On the other hand, many doctors who were prescribing the drug urged the government not to take away a new anti-diabetes treatment. At the FDA, the official who manages the agency's response to unexpected deaths from a prescription drug is Lumpkin. He also is the official directly responsible for ensuring that new drugs are reviewed and approved faster than ever before.

Dr. David J. Graham 46, a senior scientist for the FDA, spearheaded the Termites within the FDA. He warned in March 1999 that no reliable way existed to protect Rezulin patients from liver failure. Graham, whose findings were dismissed by senior FDA officials, renewed his challenge to Rezulin in January of this year.

The FDA's newfound emphasis on speed—as well as less-adversarial dealings with industry—has been pushed by lawmakers from both political parties. Pharmaceutical companies in the past have criticized the FDA for taking longer than European authorities to approve new drugs. Lumpkin and his boss, Dr. Janet Woodcock, are the two FDA officials directly responsible for meeting the agency's new objectives.

Stocky and hard-driving, Lumpkin, 46, graduated from Wake Forest University School of Medicine. He specialized in pediatric infectious disease at the Mayo Clinic and directed international research for Abbott Laboratories, a major pharmaceutical firm, before coming to the FDA in 1989. As deputy director of the FDA's Center for Drug Evaluation and Research, Lumpkin was the chief firefighter for Rezulin's wildfires.

And by the fall of 1997—seven months after its arrival on the U.S. market in March—Rezulin had become a difficult-to-contain blaze.

Patient monitoring seen as a remedy

Within three weeks of the first acknowledged liver failure cases on Oct. 10, 1997, the FDA and Warner-Lambert jointly devised a remedy: Rezulin patients should have their liver functions monitored by blood test every two to three months during the first year of use.

The FDA and the company hoped that blood testing would detect liver injury early enough to alert patients to stop taking Rezulin and avert the catastrophe of organ failure. The FDA predicted in a statement on Nov. 3, 1997, that “few, if any of these patients will go on to develop permanent liver damage if the drug is stopped.” At this point, the agency confirmed four liver failure deaths.

But less than a month after announcing this remedy, officials at the FDA learned of a disturbing development. Authorities in Britain were planning to announce Rezulin's withdrawal from the British market on Dec. 1, 1997. British officials, informed of six fatalities linked to Rezulin, had concluded that the drug's risks outweighed its benefits.

The mind-set of British authorities was detailed in a Nov. 26, 1997, e-mail message from Lumpkin to Woodcock, his superior and director of the FDA's drug review center.

“They believe that the deaths and serious toxicities are primarily seen after greater than 3 months exposure,” Lumpkin wrote in his e-mail. This analysis made “the apparent incidence of serious toxicity much greater than originally thought.”

Lumpkin told Woodcock that “unless there is some leak,” the revelation from Britain would stay sealed five more days.

The FDA, viewed for decades as upholding the gold standard for drug safety, was about to be upstaged by its counterpart, the British Medicines Control Agency. But the FDA, together with Warner-Lambert, raced to offset the pending news out of London.

Warner-Lambert maintained that the frequency of liver failure was extremely rare and insisted that the drug should remain on the U.S. market. In a Nov. 27 e-mail to the FDA, a Warner-Lambert vice president wrote:

“We are concerned about misleading physicians and patients as to the relative risk of Rezulin therapy.”

The company's position was embraced at the FDA by Lumpkin. Instead of withdrawing Rezulin, the FDA and Warner-Lambert announced a second change in the drug's labeling.

Rezulin patients were now advised to have their liver functions monitored monthly, instead of every two to three months, for the first half-year of use.

In a statement on Dec. 1, the same day that Rezulin's withdrawal was announced in Britain, the FDA said: “The increased monitoring of patients taking Rezulin is designed to detect those few patients in whom use of the drug can lead to serious liver damage.”

Five months later, tragedy struck in St. Louis with the liver failure and death of Audrey LaRue Jones, a vivacious 55-year-old high school teacher.

Jones had been monitored closely as a volunteer participant in testing of Rezulin by the prestigious National Institutes of Health. Her death on May 17, 1998, challenged the usefulness of monthly liver monitoring.

Dr. Robert I. Misbin 53, an FDA diabetes specialist, advocated the approval and the expanded use of Rezulin. Misbin seized the role of whistle-blower early this year and argued strongly for withdrawal of the drug.

Sources: FDA records, “Who's Who in America,” interviews. Compiled by David Willman and Janet Lundblad, Los Angeles Times.

"It had terrible implications for the drug itself," the FDA's Misbin said. "Because if the NIH couldn't protect a patient, then who could?"

Since the nationwide clinical trial explored whether Rezulin could prevent diabetes, none of the 580 participants taking the drug had the disease.

Within three weeks of Jones' death, officials at the NIH banished Rezulin from the clinical trial, citing safety concerns.

At the FDA, however, regulators did not broach even the possibility of withdrawing Rezulin, said several physicians familiar with the matter.

On July 28, Warner-Lambert announced that the company and the FDA had agreed to a third labeling change: Instead of monthly monitoring for half a year, patients were advised to submit to testing for the first eight months of use.

By now, 21 patients had died of Rezulin-related liver failure.

In Britain, meanwhile, authorities were considering whether to allow reintroduction of Rezulin. A doctor at the British Medicines Control Agency wrote Lumpkin on Sept. 4 requesting any "new data" showing "additional benefits" of Rezulin over other diabetes pills. A subordinate to Lumpkin responded on Oct. 16: "We do not have any recent . . . data regarding additional benefits of" Rezulin.

The British, again citing safety concerns, later refused to allow reintroduction of Rezulin. British authorities explained their position during a video conference with their FDA counterparts. According to an FDA participant, one British official said that the benefits offered by Rezulin were "nothing that isn't already there with other drugs."

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New commissioner seeks reevaluation

Newly appointed FDA commissioner Jane E. Henney ordered a reevaluation of Rezulin in January 1999, in response to a Los Angeles Times investigative series that disclosed at least 33 liver failure deaths attributable to Rezulin.

Graham, the agency's leading specialist in evaluating and preventing deaths caused by prescription drugs, was assigned the job.

Wiry, with closely cropped auburn hair, Graham, 46, is a rare breed at the FDA. He has nothing to do with reviewing new drugs. His responsibility is to examine medicines already on the market.

At a time when nearly half of all Americans regularly take one or more prescription drugs, Graham's work is of crucial importance.

Trained at Yale and Johns Hopkins medical schools, Graham's straight-arrow approach was unaffected by the rough-and-tumble of 15 years inside the FDA: Delivering bad news about a hot-selling drug could stymie a career. Senior FDA officials could not be counted on to provide support. Full-throated opposition often would come from the product's manufacturer.

While Warner-Lambert tapped an array of specialists to defend Rezulin, Graham had the assistance of one colleague, pharmacist Lanh Green. They began studying the harm done to patients, the extent to which liver-monitoring recommendations had been followed and the ongoing risks of taking Rezulin.

Within two months, Graham amassed an indictment of Rezulin. He presented his research on March 26 to an FDA advisory committee—the same panel that had unanimously endorsed the drug's approval. Among Graham's findings:

- An estimated 430 or more Rezulin patients had suffered liver failure.
- Patients incurred 1,200 times more risk of liver failure by taking Rezulin.
- One of every 1,800 Rezulin patients could be expected to suffer liver failure, a far cry from the 1-in-100,000 risk espoused by a Warner-Lambert spokesman.
- Regular liver monitoring offered no safety guarantee, in part because Rezulin could so quickly and unpredictably damage the liver, sometimes within days. And more than 99% of patients taking Rezulin for four months or longer failed to follow the liver-monitoring recommendations.

Graham also described the deaths of Audrey Jones and another woman, Rosa Delia Valenzuela, who had died in a clinical trial despite undergoing monitoring. Valenzuela, 63, of Arcadia, Calif., was struck with liver failure about a month after taking Rezulin as a participant in a Warner-Lambert clinical trial.

Warner-Lambert's representatives told the advisory committee that Rezulin could not be held responsible for many of the liver failures. They cited factors such as preexisting medical conditions.

The committee was unpersuaded by Graham and voted, 11 to 1, to recommend keeping Rezulin on the market. Three of the panelists had received compensation from Warner-Lambert or an affiliate; they were granted conflict-of-interest waivers by the FDA.

After the meeting, the FDA's Woodcock promptly distanced herself from Graham's presentation. She said that it was based on "a very broad range . . . of best guesses."

Graham also was admonished by his immediate boss for the breadth of his report to the committee, he told acquaintances. The FDA declined to allow Graham to comment for this article.

As the advisory committee members dispersed from the March 26 meeting, tragedy again was unfolding. Another Rezulin patient,

despite undergoing monthly monitoring in a Warner-Lambert clinical trial, lay near death.

Three days later, 37-year-old Adrian C. Seay died at nearby Washington Hospital Center. The District of Columbia medical examiner identified the cause of death as liver failure “following treatment with” Rezulin.

On June 16, the FDA agreed to yet another labeling change, the fourth for Rezulin.

Patients and doctors were advised that liver monitoring should be conducted monthly for the entire first year, instead of eight months. The FDA also said that new diabetes patients should no longer use Rezulin initially as a stand-alone treatment.

New recommended use for drug OKd

But the FDA was hardly renouncing Rezulin. In addition to keeping the drug on the market, the agency approved Warner-Lambert's request for a new recommended use of Rezulin, in combination with two other popular blood-sugar-lowering pills.

The FDA's handling of Rezulin was ridiculed at a June conference sponsored by Georgetown University Medical Center. Dr. Alastair J.J. Wood, a Vanderbilt University professor who also is drug therapy editor of the New England Journal of Medicine, likened the FDA's label changes to managing the risk posed by a steep cliff.

“The point was, you don't keep putting up more and more signs if people continue falling off the cliff,” Wood said. “You try to do something more definitive, like try to prevent them from falling off. You put up a fence.”

By late 1999, the tragedies persisted.

The Times disclosed on Dec. 15 that the FDA had received reports of 21 additional liver failure deaths since Graham's presentation. Graham, acting with the knowledge of his supervisor, began preparing an updated analysis.

At the start of the new year, Graham told his fellow Termites that he was readying a knockout blow of Rezulin. He had amassed a case so strong that no one at the FDA could resist any longer.

Or so Graham hoped.

On Jan. 6 of this year, Graham shared his latest findings regarding Rezulin's toll at an FDA staff meeting. In attendance was Dr. Robert J. Temple, one of the agency's most respected scientists. As director of one of the FDA's five drug-review offices, Temple was a subordinate, on paper, to Lumpkin and Woodcock. But his reputation, built over 28 years inside the agency, was without peer. In a room of mostly mid-level medical officers, Temple's every word and gesture counted.

First, he raised the precedent of the “imminent hazard” withdrawal in 1977 of Phenformin, the diabetes drug Misbin had dealt with at Ceiba-Geigy.

This was useful context. But where, his colleagues wanted to know, did Temple stand on Rezulin? All eyes were fixed on him.

Temple briskly slashed two fingers across his throat.

Specialists asked to look at two other drugs

As the session ended, the Termites were emboldened. A consensus had formed for Rezulin's prompt withdrawal.

But any such hope was doused on Jan. 13, when Lumpkin met with the same FDA specialists.

Lumpkin directed them to shift focus and assess the safety of two newer chemical cousins of Rezulin. The FDA had granted rapid approval to these diabetes drugs, Avandia and Actos, in mid-1999 after they were found to be far less toxic to the liver.

Several FDA physicians viewed Lumpkin's approach as diversionary. Rezulin, they said, should stand or fall on its own merits.

Lumpkin created further delay by scheduling two private meetings between FDA staff members and Warner-Lambert executives on Feb. 2 and March 1.

At the first meeting, Graham pointed out that the FDA had received reports of liver failure among patients who had taken Rezulin for eight to 18 months. This clashed with the company's earlier claim that the risk “substantially declines after six to eight months of therapy.”

"How many more unnecessary deaths will it take before you take action?" Misbin asked the company.

Some of the most pointed questions came from Temple and Misbin. They were skeptical of the company's claims that liver monitoring worked.

As of early February, the FDA press office confirmed 85 cases of liver failure, including 58 deaths. This was nearly twice the number of liver failures acknowledged by the FDA a year earlier.

Nevertheless, the FDA brass continued to endorse Rezulin.

On Feb. 24, Woodcock issued a statement reaffirming the agency's confidence in the drug, saying that "in many patients it has proven to be very effective." Her remarks showed that Rezulin continued to enjoy deep and well-connected support.

And doctors kept prescribing the drug. According to the pharmaceutical information company IMS Health, Rezulin during the preceding year generated \$674 million in sales.

"People who felt that the drug was too risky really shouldn't have prescribed it," Woodcock said in an interview. "The information was available to them. . . . Everything we've done [has been] out in the open."

FDA session with firm seen as pivotal

The Termites, their ranks now swollen to about a dozen agency specialists, did not retreat. They made known to colleagues their conclusion that Rezulin should be withdrawn.

The March 1 meeting with Warner-Lambert loomed pivotal. The Termites were bracing for more resistance from the top. Senior FDA officials were determined to keep the session shrouded in confidentiality.

Saying that they suspected a Times reporter was inside the agency's high-security headquarters in Rockville, Md., officials at midday shifted the 4 p.m. meeting a few miles north, to a conference room next to the sixth-floor offices of Woodcock and Lumpkin.

Behind closed doors, Lumpkin broached the option of bringing Rezulin for a third time to the FDA advisory committee, the panel that had overwhelmingly endorsed the drug in December 1996 and again in March 1999.

Lumpkin's suggestion, several participants said, meant that the drug might stay on the market indefinitely.

Warner-Lambert proposed that Rezulin remain on the market for as long as two years while the company conducted new studies measuring the frequency of liver failure.

Dr. Solomon Sobel, until recently director of the FDA's endocrine drug division, questioned the company's claim that doctors and patients at last had complied with the monitoring recommendations.

Sobel, a hulking, soft-spoken man, had helped supervise the original fast-track approval of Rezulin. Now he too was telling colleagues that the drug should be withdrawn.

Another mid-level medical officer with responsibility over diabetes drugs, Dr. Saul Malozowski, also joined the Termites in pushing for Rezulin's withdrawal.

Lumpkin indicated to Warner-Lambert that no regulatory conclusion had been reached. But, Lumpkin made clear afterward, he was unconvinced that withdrawal of Rezulin was warranted. On March 2, one day after the meeting, Lumpkin wrote in an e-mail that his subordinates were relying on "soft hypotheses."

Lumpkin then left the agency for several days, traveling to the French Riviera for a meeting of the Drug Information Assn., an industry group on whose board he sits.

The Termites feared the FDA would stand pat and that avoidable deaths would continue.

By March 3, Graham had seen and heard enough.

He dropped a bomb: an e-mail addressed to Lumpkin and 13 other FDA officials. Graham's message could embarrass, if not render untenable, the position of Rezulin's defenders.

He wrote that Warner-Lambert's claims of safety, long accepted by senior FDA officials, were "contradicted" by the scientific record.

"There are no existing data anywhere to suggest or support the hypothesis that monthly monitoring can or in fact does prevent

drug-induced liver failure,” he declared. “This idea, translated into policy through labeling, is entirely unproven and represents an imagined, artificial hope, not reality.”

Graham concluded:

“At each juncture in the management of Rezulin’s liver failure risk, hindsight shows that we had little or no effect and that [Warner-Lambert’s] assertions that the liver failure problem was solved, were proved false. . . . The data at hand should persuade us that Rezulin is unsafe compared to other available therapies and that its marketing be stopped.”

Doctor takes on role of whistle-blower

Until early March, the Termites had confined their opposition to within the FDA.

That was about to change.

Misbin, the longtime champion of Rezulin, had concluded that the drug must go.

“I consistently underestimated the rapidity with which Rezulin could damage the liver . . . ,” Misbin recalled in a recent interview. “I have underestimated the virulence of Rezulin.”

Misbin seized the role of whistle-blower. He reached for an audience the FDA could not ignore: Congress.

Misbin wrote to Rep. Henry A. Waxman (D-Los Angeles) and seven other lawmakers. He turned over internal e-mails regarding the agency’s handling of Rezulin. He shared damning correspondence sent to him by a St. Louis physician who conducted early research for Warner-Lambert.

The doctor, Janet B. McGill, alleged that the company “deliberately omitted reports of liver toxicity and misrepresented serious adverse events experienced by [Rezulin] patients in their clinical studies.”

Misbin soon, however, found himself under an FDA internal-affairs investigation for allegedly disseminating confidential agency materials. The inquiry was initiated based on a complaint by Warner-Lambert that “someone had leaked nonpublic information” from agency files, according to Melinda K. Plaisser, an FDA associate commissioner.

On March 13, a senior FDA official warned Misbin:

“You are required to cooperate with the investigation and failure to cooperate may result in disciplinary actions up to and including dismissal from federal service.”

Misbin was undeterred. He refused to answer investigators’ questions unless they were posed in writing.

Another agency medical officer, 72-year-old Dr. Leo Lutwak, also was targeted. Two internal affairs agents asked Lutwak if he had given The Times a Jan. 24 e-mail written by Misbin. After the interrogation, Lutwak said, the agents warned that if his statements were proved to be untruthful he was at risk of imprisonment.

First the defrocking of Gueriguian. Then the admonishing of Graham. Now an investigation of Misbin and Lutwak. For many inside the FDA, the message was unmistakable: Oppose Rezulin at your peril.

## FDA briefing yields no pronouncement

The FDA at this point had linked 89 voluntarily reported liver failures, including 61 deaths, to the use of Rezulin.

On March 15, Woodcock and Lumpkin were summoned to the 14th-floor office of FDA Commissioner Henney for a confidential discussion of Rezulin.

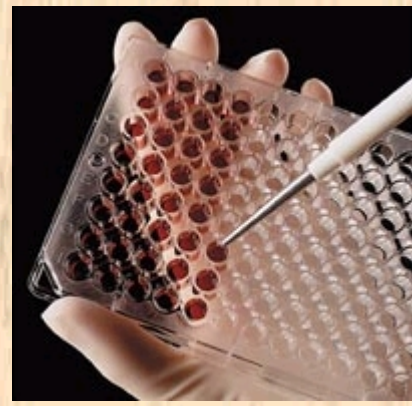
On the job since June 1998, Henney had said virtually nothing publicly about Rezulin. Her detachment contrasted with her predecessor, Dr. David A. Kessler, whose activism made him a formidable national figure.

Following the briefing, Henney again made no pronouncement about Rezulin. The drug's day-to-day fate remained in the hands of Woodcock and Lumpkin. They scheduled another staff meeting to discuss Rezulin.

For the Termites, this was perhaps their last chance.

At 2:30 p.m. on Tuesday, March 21, Woodcock, Lumpkin, Misbin, Graham, Temple, Sobel and nearly a dozen other agency specialists gathered for a round-table discussion at the FDA's "Woodmont 2" office building in Rockville.

Graham focused on how, in his view, patients incurred increased risk of liver failure the longer they stayed on Rezulin. He estimated that 20 liver failures were occurring each month.



## A Remedy Without Merit?

As the number of deaths among Rezulin users escalated over a 29-month period, the FDA issued four separate recommendations for blood testing, called "monitoring," to safeguard patients from liver failure. But no scientific proof existed then, or now, that monitoring would protect patients.

After two hours, Woodcock adjourned the meeting without declaring her or the agency's position. She then huddled in her office with a handful of subordinates, including Lumpkin and Temple.

The moment reflected more than one drug's destiny: Lumpkin and Woodcock had captained the FDA's shift to accelerated approvals and less-adversarial relations with drug companies, a new paradigm epitomized by Rezulin.

Date: Nov. 3, 1997

Toll: [1] death

FDA remedy: Recommended liver testing within the first two months of treatment and then every three months during the first year of use.

By this point, the FDA had overseen the withdrawal of seven medications in 2½ years. The fate of Rezulin posed unique sensitivity: It was the only therapy approved on a fast-track--and by the same FDA officials who were now sitting in final judgment of the drug.

Lumpkin and Woodcock had cited the absence of more withdrawals as evidence

Date: Dec. 1, 1997

Toll: 4 deaths

FDA remedy: Recommended liver testing every month for the first six months of use and then every other month for the next six months.

that the agency's faster approvals were not compromising safety. The steady, if not declining, rate of withdrawals is particularly reassuring," they wrote in a May 1999 issue of the Journal of the American Medical Association.

All of which meant that, if Lumpkin and Woodcock sought the withdrawal of Rezulin, they risked further discrediting the FDA's faster, less-adversarial approach.

Date: July 28, 1998

Toll: 21 deaths

FDA remedy: Recommended liver testing monthly for the first eight months and then every two months for the remainder of the first year.

For Rezulin, the agency had confirmed 63 liver failure deaths by the deliberations of March 21.

Nightfall was approaching. Lumpkin made one last attempt to avert Rezulin's immediate withdrawal, according to officials familiar with the discussion. He suggested scheduling another meeting with the advisory committee to reassess Rezulin. Temple objected, saying that more delay was unjustified.

The decision was now Woodcock's. It had been 29 months and 11 days since the FDA received the first reports of liver failure. She phoned executives at Warner-Lambert's headquarters in Morris Plains, N.J.

By 7:30 p.m., the FDA issued a statement disclosing that the company had agreed to immediately withdraw Rezulin. In the statement, Woodcock observed:

"We are now confident that patients have safer alternatives."

Date: June 16, 1999

Toll: 35 deaths

FDA remedy: Recommended liver testing monthly for the first year, then quarterly. FDA no longer recommends Rezulin as an initial treatment for diabetes.

Times researchers Janet Lundblad in Los Angeles and Sunny Kaplan in Washington contributed to this story. Story originally appeared in the L. A. Times. Copyright, 2000, Los Angeles Times. Reprinted with permission.

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