

4: TOO SWEET TO BE TRUE

Irving Motek, a forty-three-year-old baker with diabetes, went to see his doctor for a routine checkup. He had been getting a little sloppy with his diet, and as a result his blood sugar was running a bit high. To address the problem his doctor stopped his old diabetes medicine and began a new one. A few weeks later, Irving felt like he was coming down with the flu; his wife noted his skin had become sallow and his eyes looked yellowish. He became progressively more lethargic, was hospitalized, and found to be in profound liver failure. Two weeks later he was comatose and terminally ill. To survive, he required a liver transplant to replace his own severely damaged organ. Eleven days later a twenty-three-year-old motorcyclist took a curve too fast, hit a patch of ice, and rammed his helmet-free head into the guard rail of the interstate at seventy miles per hour, denting the rail and shattering his skull. On arrival at the hospital the biker was diagnosed as brain-dead and his family agreed to donate his organs.

With a new liver, Irving recovered slowly over two more months in the hospital. He was eventually discharged home in stable condition on a combination of drugs to suppress his immune system; he'd need to take them along with a different diabetes medicine for the rest of his life.

Since 1990, more major drugs have been withdrawn for substantial unexpected safety problems than ever before in such rapid succession. Sometimes this has been the result of premarketing studies that were too small to detect important but rare side effects. Some of the problems may have stemmed from FDA's attempts to speed up its approval process. But as we saw with Pondimin and Redux, in some instances the disaster was brought on by willful underestimation of a drug's known risks. This also seems to be what happened with Rezulin, the first in a new class of diabetes medications first marketed in March of 1997.

All of us in medicine would like to believe that the discovery of a new drug is the end product of a disciplined, purposeful search that begins with an insight from biochemistry or physiology and continues over years in the lab: scientists pore over test tubes or rats or printouts of genetic data, and then a dedicated investigator's spark of analytic brilliance catalyzes the final eureka. Sometimes it really works this way, but often the origins of a breakthrough drug are much more humble.

Viagra, for instance, was being developed as a treatment for heart disease until a few serendipitous observations came together. In clinical trials, to the embarrassment of both staff and patients, nurses going from bed to bed to measure blood pressures noticed that male study subjects often had large erections. Although the experimental product's cardiac benefits were unimpressive, men given it asked if they could please continue taking the drug after the study ended. (As a heart drug the product didn't show exceptional performance, but its recipients did.) Cardiologists and their male patients sometimes differ on which is the most important organ in the body; although Viagra didn't do much for one it excelled in the other, and was rechristened as a treatment for erectile dysfunction.

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Another product that switched identities was minoxidil. It was developed to lower blood pressure but wasn't well tolerated in clinical trials. Many patients who took it complained of an annoying side effect—excessive hair growth. It was later marketed as Rogaine to treat baldness.

Despite the appealing image of the focused, white-coated pharmaceutical researcher so compellingly portrayed in TV commercials, the initial evolution of the diabetes drug Rezulin also owed much to serendipity. An earlier compound called ciglitazone, the first drug in a new chemical class, was being tested as a potential cholesterol-lowering compound. But what it really lowered was subjects' blood sugars, often excessively—a side effect that rendered it useless for its intended purpose. A second reason ciglitazone was not developed further was that it was toxic to the liver, an observation that will be important later. But the experience led to the insight that similar compounds might prove useful in the management of diabetes.

The first product of this kind that made it to market was its cousin troglitazone, trade named Rezulin. (It's much more appealing for a drug to have a name that suggests resolution of a problem, rather than evoking images of troglodytes.) Most other oral drugs for adult-onset diabetes worked primarily by flogging the patient's exhausted pancreas to make more insulin, or by persuading the liver to release less glucose. When all else failed there was always insulin itself. But this novel class of drugs caused the liver to produce less glucose and rendered fat cells more sensitive to the effects of insulin, either the body's own or the kind given through a syringe. The physiological rationale for this new double-barreled approach was compelling.

Troglitazone was granted fast-track review by the FDA, a process developed around 1990 after AIDS activists terrified the agency with a massive sit-in to protest the government's inability to approve lifesaving breakthrough products quickly enough. As per usual FDA policy, the manufacturer was not required to demonstrate that Rezulin was better than any existing drug. Studies were conducted in which diabetic patients whose blood sugar was poorly controlled with insulin had either Rezulin or placebo added to their regimens. Not astonishingly, the new drug lowered blood sugar better than placebo did. Its initial approval hinged on premarketing studies involving only about 2,500 patients.

A MISLEADING BEGINNING

Based on this evidence, an FDA advisory committee met in December 1996 to decide whether the drug should be approved for sale. In summarizing the product's safety profile at that meeting, a doctor representing the manufacturer, Parke-Davis, reported that its clinical trials showed that the drug's risk of liver toxicity was "comparable to placebo." The company also had collected additional safety data from other studies, but these were not presented at that meeting. Instead, the Parke-Davis physician said that the rate of liver damage in those other analyses was "very, very similar" to what was reported at the approval hearing, and that he would provide that data to FDA later on. Based on the data presented that day, the advisory committee voted to allow the drug onto the market. As it turned out, the rate of clinically important liver damage in those early trials had been considerably higher in the patients who had gotten Rezulin rather than placebo. But as a cynical sports commentator once observed, "The rules are defined by what the ref sees."

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The company did provide FDA with the promised data from the additional trials a week after the approval. It revealed a rate of liver abnormalities that was not at all “very, very similar” in the patients who got the new drug; it was substantially greater. But the drug had already been approved and the new information didn’t receive widespread attention.

Rezulin’s initial approval required that it be used only for patients already taking insulin, limiting its potential utilization and thus its market share. But Parke-Davis quickly sought further permission to market the drug as a stand-alone therapy for diabetes. This would greatly increase the product’s commercial potential, but would also expose far more patients to its risks. Backed by a huge marketing campaign featuring its novel mode of action, sales of Rezulin took off. But by October 1997, when it had been on the market for just eight months, concern began to grow over a steady flow of reports describing patients who developed severe and unexpected liver damage while taking the drug. In preparation for a meeting with the FDA on October 24, Parke-Davis ran a computer tabulation of all subjects in its early premarketing clinical trials whose blood tests suggested liver abnormalities. But before a company physician reported these findings to the FDA, he tightened the criterion for “abnormal” in patients who got the new product but not for those in the placebo group, obscuring the elevated risk. Parke-Davis then obtained FDA permission to use the lower number of liver cases in its official product warnings, without revealing that the initial estimate had been considerably larger.

Normally, we estimate a drug’s potential for liver damage by measuring whether enzymes from that organ leak into the bloodstream. This blood test is a useful indicator of the severity of liver damage: normal levels are reassuring, modest elevations (three times the normal range) raise questions, and much higher levels (as high as ten or twenty times the normal range) are usually a sign of substantial damage. But in reporting these results to the FDA, companies sometimes fold together all abnormal liver tests under the broad category of “greater than three times normal,” even if a large proportion of such patients have elevations that were far higher—a clear sign of widespread liver cell destruction. This is akin to asking your child how his day went at school and being told that he had a squabble with the teacher, when in fact he had hacked her to death with a machete. A fair report of the event would have mentioned something about stab wounds and not merely categorized it under the rubric “squabble.”

By the autumn of 1997, 135 cases of severe liver damage had been reported in Rezulin patients, including at least five that were fatal. All the cases had occurred in the United States or Japan. Drug safety surveillance is an international field, and news about adverse events in one country is rapidly communicated around the world. Looking back, that period provides a fascinating contrast in how regulatory authorities and companies in different countries can assess the very same data and come to vastly different conclusions.

The drug was approved for use in the United Kingdom a few months later than in the United States. It was sold there under a licensing agreement with the British pharmaceutical firm Glaxo-Wellcome, which did not begin marketing it until September 1997. Within six weeks, Glaxo officials in London became concerned about the rapidly increasing rate of reports of liver damage. The affected patients often had nothing in their histories to suggest that they would be susceptible to this life-threatening problem. It was also becoming clear that stopping the drug when the problem was first detected

sometimes was not enough to reverse the damage. New reports of liver disease were continuing to come in from the United States at an accelerating rate. No one could be sure when the tide of toxicity would crest.

The British company concluded that with so many safer options available to treat diabetes without damaging the liver, the drug's risk-benefit relationship was indefensible. In late November 1997 Glaxo notified the British government that it intended to take its product off the market as of December 1, after only three months of sales. Over the next two weeks Glaxo and the Japanese company that had initially developed the product withdrew applications to market Rezulin in twenty-six additional countries from Iceland to Israel, including virtually all of Europe.

TRANSATLANTIC DIFFERENCES

At that moment, in the United States, Parke-Davis was taking a completely different course. On December 1, as Glaxo was removing the drug from pharmacies throughout England, Parke-Davis sent a letter to every practicing physician in America. It reminded doctors to monitor liver function closely in patients taking the drug, and explained that "heightened awareness following the earlier labeling change [recommending more frequent blood tests of liver function] has, as expected, generated some additional reports of hepatic dysfunction." The company admitted that its partner Glaxo had decided to "temporarily suspend marketing" of the drug in Britain "pending their review of worldwide safety data," but added that Glaxo "has experience with only 5,000 patients" on the drug in Great Britain, a number much smaller than Parke-Davis' experience in the U.S. market. This was misleading; although sales in the United Kingdom were smaller, Glaxo's withdrawal decision had been based on liver toxicity data from all over the world, not just events in Britain. Indeed, most of the adverse events on which the decision was based had occurred in the United States.

Parke-Davis' December letter to physicians went on to report that together with the FDA, it had "already completed a thorough review of the worldwide safety experience with Rezulin." In bold type it declared, "You will be reassured to know that the additional reports received since early November do not indicate a greater frequency of liver injury or potential for serious harm than had been previously estimated. . . ." and continued, "The FDA continues to find a favorable benefit to risk relationship for Rezulin therapy. . . ." The letter reminded doctors that all treatments for diabetes could cause severe side effects, and ended by recommending close monitoring of patients with once-a-month blood tests to detect liver problems.

During that same week at the end of 1997, researchers at the federal National Institutes of Health were hit with their own piece of the Rezulin crisis. Encouraged by Parke-Davis, the NIH had gone out on a limb by initiating a government-sponsored study that used Rezulin not to treat diabetes but to keep it from developing in healthy patients who appeared to be at risk of becoming diabetic. At a cost of \$150 million, it was to be the government's largest diabetes study ever. But now NIH was in the awkward position of administering a potentially fatal drug to patients who didn't even have the disease it was approved to treat. The doctors responsible for the trial worried what effect the British decision might have on U.S. physicians who had enrolled their own patients in the study. On November 28, a letter was sent to participating physicians by Dr. Richard Eastman,

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director of the NIH Division of Diabetes, Endocrine, and Metabolic Diseases. As one of the NIH's top diabetes researchers, he had major responsibility for the design and ongoing conduct of the trial, including the original decision to include Rezulin, as well as the decision now on how to proceed. His letter began by noting that Glaxo's decision to withdraw the drug in England was "apparently a marketing decision, rather than a regulatory decision." The NIH, he reported, "is comfortable continuing with the troglitazone arm of the study despite the decision by Glaxo to withdraw the drug in Europe."

I had known Eastman years earlier, when as young physicians we were both in training at the Beth Israel Hospital in Boston. I recalled that he was a conscientious and talented clinician with a keen interest in endocrinology. I had been proud to learn that my former colleague had risen to become one of the most senior diabetes researchers at NIH. I was not proud to learn that he was also serving as a paid consultant to Parke-Davis at the same time that he was overseeing the design and conduct of the Rezulin study, having accepted over \$78,000 from the company through 1997. According to government documents, a lawyer for the Department of Health and Human Services had warned him in 1996 that this represented a conflict of interest, but the relationship was not acknowledged publicly until it was reported in late 1998 by David Willman of the Los Angeles Times. Interviewed by Willman, Eastman's immediate superior at NIH said he saw no conflict-of-interest problem. According to the respected journal *Nature*, the university-based chairman of the study also saw no problem, explaining that virtually all medical researchers in and out of government had such consulting relationships with industry. Willman reported that "in his defense, Eastman said that over the last six years he had consulted for five other drug companies" in addition to Rezulin's manufacturer while shaping and overseeing NIH's portfolio of diabetes research. What a defense.

In May 1998, six months after Dr. Eastman's letter of reassurance to physicians, a previously healthy Illinois teacher who had been given Rezulin in the NIH diabetes prevention study developed fulminant liver toxicity. Her illness came on rapidly: despite frequent monitoring of blood tests just as the company required, the problem developed too suddenly to detect. Once discovered, it proved to be irreversible; she was soon dead. Parke-Davis issued a statement that the fatality had nothing to do with its drug, but the NIH concluded otherwise. Her case, and others like it, made it hard to take comfort in the idea that regular blood tests could nip the problem in the bud. This was the same conclusion the British had come to a year and a half earlier when they withdrew the drug from the market. Within a month of the teacher's death, NIH terminated the Rezulin arm of the diabetes prevention trial. But the drug remained in widespread use in routine clinical practice in the United States for nearly another two years.

In October 1998 the Australian equivalent of the FDA refused to give initial approval to Rezulin because of its safety record and doubts that the drug could be monitored closely enough to prevent irreversible liver damage. A similar position was taken by New Zealand's drug review body two months later. Back in the United States, Parke-Davis still continued to argue that careful liver function testing could detect problems in time for the drug to be stopped, preventing major damage. But it was becoming clear to most observers that this was implausible. More reports were coming in of Rezulin patients who suffered liver damage so rapid and devastating that even monthly

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blood tests could not have spotted it coming. In a number of them, the damage continued apace even after the drug was stopped.

No one who has ever been within a hundred yards of a typical medical practice should have expected that physicians and patients would consistently follow the demanding monthly blood test schedule Parke-Davis suggested. My research unit had taken a look at how well physicians monitored patients prescribed tacrine, a weakly effective drug for patients with Alzheimer's disease. It was also manufactured by Parke-Davis, and also caused liver damage. There, too, the company had told doctors that the damage could be prevented by frequent blood tests to measure liver function. We scanned the records of several thousand patients prescribed tacrine and found that only a tiny fraction were actually getting the blood tests as the company recommended. Later on Dr. David Graham, an FDA epidemiologist, analyzed data from a large HMO to see whether patients given Rezulin in typical practice were actually being monitored as required. He found that by the third month of use, fewer than 5 percent of them were getting all the recommended blood tests. This "monitoring defense" reflected the supine posture often adopted by both drug manufacturers and the FDA throughout the 1990s: "We told you there was a risk, we put it in the official label, so it's not our fault if something bad happened."

Near the end of 1998, another patient enrolled in a different company-sponsored Rezulin study developed rapid-onset liver failure despite regular monitoring; within a month she was dead. But over 2,600 other patients throughout the country were still participating in that study. Parke-Davis had paid physicians a fee of up to \$350 for each patient they enrolled. One Parke-Davis scientist asked in a memo, "Do we have to send a letter out to all of the REACH investigators to inform them of this event?" No, responded her colleague at the company, using capital letters to underscore the point. "We have NO REGULATORY OBLIGATION to send a letter to the [study] physicians . . . to send out a letter now would be misleading because we cannot fully explain the case and it would be unnecessarily frightening." The company blamed the death on other causes, and continued to claim that the drug was safe as long as liver function was monitored. In the industry this is sometimes known as "defending the molecule."

In March 1999, over a year after troglitazone had been withdrawn in Europe, the British Medicines Control Agency took a second look at the drug and ruled that it should remain off the market because the evidence showed that it could not be used safely. That same month in the United States, the FDA Advisory Committee on Endocrinologic and Metabolic Drugs was scheduled to meet again to reassess Rezulin in light of the new reports of liver failure that continued to come in. At the time, it seemed clear to many of us that even though the U.S. authorities had failed to grasp the severity of the problem when it first developed, this meeting would provide an opportunity to review all the data and finally come to the right decision. There were by now even more cases of severe liver failure in patients given Rezulin, including several deaths and emergency liver transplants.

Astonishingly, the FDA's advisory committee again recommended that the drug remain on the market. It suggested that its use as sole therapy for diabetes be curtailed, but approved its continued availability for diabetics taking insulin.

On hearing of the FDA decision I remember feeling the sensation people often have in dreams, watching a car or plane or train speeding along and knowing it's about to

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crash. You try to scream but can't make a sound. I recall walking around the hospital that day, asking anyone who would listen, "What the hell are those people doing?!" I was able to make some sound, though. I proposed that despite the FDA decision our hospital should stop using Rezulin. The Brigham's Pharmacy and Therapeutics Committee agreed, and we removed the drug from use at our institution.

The FDA medical officer assigned to the Rezulin case, Dr. Robert Misbin, also tried to make a sound. Frustrated at his agency's unwillingness to act decisively, he began a personal crusade unusual for a government worker. He later stated that if he had been aware of the evidence of liver damage already in place when Rezulin was first evaluated by the FDA, he would have been much less willing to see it approved, and would have vehemently resisted accepting its wider use as a first-line therapy for diabetes. Over the coming months, Dr. Misbin vaulted over his bosses' heads and sent anguished letters to congressmen, urging them to act even if the agency would not. In a letter to Representative Henry Waxman, he wrote:

I have been frustrated in my efforts to convince [FDA] management that the time has come to remove Rezulin from the market. . . . Were this a question of drug approval, FDA would have taken action in six months to meet the user fee goal [of speeding up approvals] mandated by Congress. But since the question is withdrawal of a marketed product, there seems to be no time limit. I am enclosing . . . documentation of Parke-Davis' reluctance to bring to public attention the risk of liver toxicity that they found in their clinical trials.

The "user fee goal" refers to a reorientation of the agency that occurred in the 1990s in the wake of the enactment by Congress of the Prescription Drug User Fee Act, known as PDUFA (rhymes with "palooka"). That law provides for drug companies to pay the agency a fee to have their products evaluated, averaging about a half-million dollars per drug. These funds are then used to pay for the person-time expended by the FDA employees reviewing the evidence. Critics have argued that this can distort the review process, a concern illustrated by the conversation another FDA scientist had with a senior agency official. His concerns about the safety of a particular drug had attracted the ire of its manufacturer.

"You need," his boss told him, "to understand that the pharmaceutical industry is our client."

"That's odd," he responded. "I always thought our clients were the people of the United States."

John Ashcroft was still a senator from Missouri as the Rezulin story was unraveling. In writing to him, Dr. Misbin described a letter he received from a St. Louis physician who claimed that Parke-Davis had omitted data about Rezulin-related liver damage from its reports to FDA, and that FDA was ineffective in dealing with the problem. "I believe that [her] complaint about FDA is well founded," Dr. Misbin wrote. "There is little doubt that patients are still experiencing Rezulin-related liver toxicity because of FDA's inaction. In the absence of a threat of Congressional hearing, I see little hope of turning this around until many more patients have died."

A BELATED INSIGHT

One full year after the follow-up advisory committee meeting that again endorsed the continued use of Rezulin, FDA eventually reconsidered its decision. The committee finally recommended in March 2000 that the drug be taken off the market. More than two years after the same decision was made in England, over \$2 billion in sales and ninety-four cases of acute liver failure (sixty-six of them fatal) after its introduction, Rezulin ended its blockbuster career in the United States.

The courts are still considering how much of the Rezulin tragedy was produced by willful malfeasance versus what could be called passive-aggressive surveillance: foot-dragging in following up on signals of a potential hazard. As scores of cases approached trial, the manufacturer's zeal to protect its molecule instead of patients followed what could be called the FDA defense, a gambit seen in many drug product liability suits. In that strategy, a company maintains a bare-bones adverse-events reporting department, staffed on the front lines by people with little or no training in epidemiology or clinical matters. Once its drug is approved for marketing, the company doesn't proactively investigate how appropriately it is being used, or what side effects occur in patients who take it. When reports of those adverse events are nonetheless sent in spontaneously by doctors or patients, the company passes them along to the FDA as required by law, with minimal or no further scrutiny. It's widely known that the FDA division on the receiving end of these reports has traditionally been underpopulated and overworked, partly because of earlier industry opposition to allocating any of its user-fee funds to support those activities. Eventually, if an important side effect does surface, company officials can respond as many have in court, saying, in effect: "We didn't notice a worrisome pattern. We obeyed the regulations and sent FDA all the reports we received. They never made us do a study, or send out a warning, or take the drug off the market. So it's not our fault if anyone got hurt." This is the corporate equivalent of a teenager murdering both his parents and then begging the court for mercy on the grounds that he's an orphan.

How very . . . twentieth century. Case after case of multimillion-dollar adverse-event settlements involving withdrawn drugs have demonstrated that this just isn't going to be good enough anymore. Ignorance of the flaw is no excuse.

In a trenchant postmortem of the Rezulin story published in the British medical journal *Lancet*, Dr. Edwin Gale, an English diabetes specialist, argued that Rezulin had never been a drug of especially great value in the first place. He pointed out that testing it against placebo in diabetic patients was a very low standard to meet. Further, even though safer products from this new class of drug had been introduced in the years following Rezulin's withdrawal, the subsequent clinical experience with them had not borne out manufacturers' claims that they would transform the care of diabetes. "Troglitazone came and went with no demonstrated advantage over existing therapy," he wrote. But because mere advantage over placebo was all that was required for approval, not head-to-head comparisons with standard therapy, "the system did not require the studies that would have allowed us to find out." He continued:

The regulatory process creates an evidence-free zone at the time of launch of new drugs. Companies need to market aggressively during this period because the countdown on the life of their product licence has already

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begun. Even the most ethical company will be reluctant to launch studies which might discredit a marketing claim based on weak evidence. . . .

A physician does, however, differ in important respects from a travel agent, or so many of us believe. But who speaks for the clinician? Oddly enough there is no answer to this. . . . Access to information about new drugs is closely retained by the companies, and post-marketing studies are dictated by marketing policy. . . . One lesson from [Rezulin] is that the public interest is not well served by the current system of drug development.