WHAT GLAXO KNEW ABOUT ZANTAC

THE WORLD'S BESTSELLING HEARTBURN MEDICATION DIDN'T JUST CONTAIN A PROBABLE CARCINOGEN—IT CREATED IT. COURT DOCUMENTS SHOW THE DRUG'S MAKER DOWNPLAYED CRUCIAL INFORMATION FOR 40 YEARS

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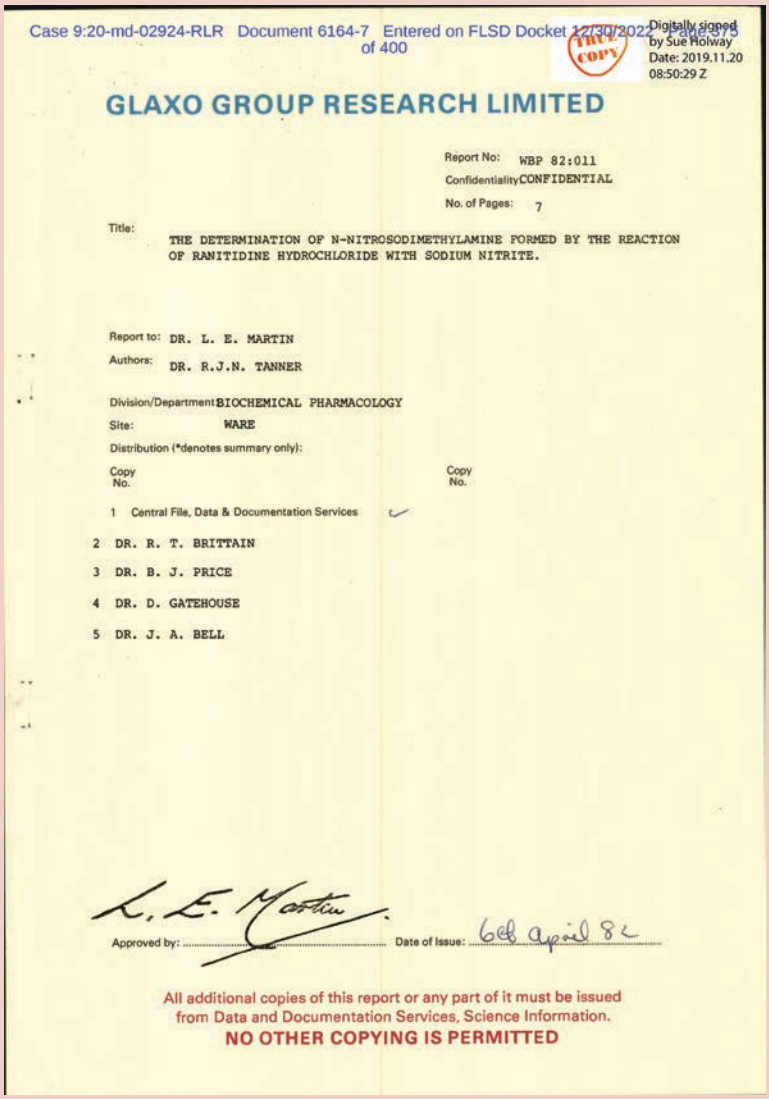
The small British company was sometimes called Glaxo University, because it conducted important pharmaceutical research that rarely resulted in profitable drugs. Then the scientists at Glaxo Laboratories created a molecule they called ranitidine, and in 1978 the company was granted a US patent. The molecule was new, but not novel. The scientists had, as scientists sometimes do, looked for a way to mimic the success of an established drug—in this case, one that healed ulcers and could be used to treat heartburn. They developed ranitidine quickly, and the US Food and Drug Administration reviewed it quickly. Glaxo gave it the brand name Zantac.

Glaxo marketed it as better and safer than the drug that inspired it, Tagamet, and before long, Zantac overtook Tagamet to become the world's bestselling prescription medication. For years, Glaxo counted on Zantac for nearly half of its sales and almost as much of its profit. The company won an award from Queen Elizabeth; the chief executive officer was knighted. Zantac created reputations and fortunes. It financed the modern version of Glaxo, which, after mergers and takeovers and spinoffs, ended up as GSK Plc, a company now worth some $73 billion. Among its most popular drugs are the antidepressants Paxil and Wellbutrin and the shingles vaccine Shingrix.

But not Zantac. In 2019 the drug was found to be tainted with high levels of a probable carcinogen. Not by chance or mistake in a few batches. The poison is created by ranitidine itself. Zantac's makers and health regulators around the world recalled the drug, and in the spring of 2020 the FDA forced it off the market altogether. No company could manufacture it; nobody should ingest it. The carcinogen, called NDMA, was once added to rocket fuel and is now used only to induce cancer in lab rats. The FDA says consuming minuscule amounts isn't harmful. But tests were revealing excessive amounts of NDMA in ranitidine—and a capacity to create even more over time. No version seemed safe.

From the beginning to the end of ranitidine, Glaxo had been warned by its own scientists and independent researchers about the potential danger. An account of those four decades emerges in hundreds of documents, thousands of pages, many of which have never been made public. *Bloomberg Businessweek* reviewed court filings, many still under seal, as well as studies, FDA transcripts and new drug applications obtained via Freedom of Information Act requests. They show that the FDA considered the cancer risks when approving ranitidine. But Glaxo didn't share a critical study. Over the years, the company also backed flawed research designed to minimize concerns and chose not to routinely transport and store the medication in ways that could have eased the problem. Glaxo sold a drug that might harm people, tried to discount evidence of that and never gave anyone the slightest warning.



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The Tanner report, which Glaxo kept under wraps for almost four decades

More than 70,000 people who took Zantac are suing the company in US state courts for selling a potentially contaminated and dangerous drug. The first of those trials is supposed to begin in late February in the California Superior Court in Alameda County but will likely be postponed until summer to accommodate the judge's schedule. Other companies that sold Zantac in later years, including Pfizer Inc. and Sanofi, are also part of the lawsuits.

In December, GSK won a favorable ruling in a separate group of cases in federal court. US District Judge Robin Rosenberg, in the Southern District of Florida, dismissed thousands of federal lawsuits that had been consolidated in her courtroom for pretrial proceedings. She declared that there is "no widespread acceptance in the scientific community of an observable, statistically significant association between ranitidine and cancer." GSK considers Rosenberg's the final word on those claims. "The court's view is consistent with the position that GSK and other co-defendants have taken throughout this litigation," Kathleen Quinn, a company spokesperson, said in

GABBY JONES/BLOOMBERG (2). REPORT: GSK, ZANTAC (RANITIDINE) PRODUCTS LIABILITY LITIGATION

a statement. “After more than three years of extensive study—including 13 peer-reviewed epidemiological studies conducted looking at human data regarding the use of ranitidine—the scientific consensus is that there is no consistent or reliable evidence that Zantac (ranitidine) increases the risk for any type of cancer.” Lawyers representing those who brought the suits plan to appeal.

GSK does still have to fight the tens of thousands of cases waiting in state courts, where judges aren’t bound by the federal court’s ruling. The company said in a statement that it “will continue to defend itself vigorously, including against all claims in this litigation.” GSK declined to comment further.

Every public-health agency, from the Environmental Protection Agency to the FDA to the World Health Organization, says NDMA likely causes cancer in humans. But proving that a particular person’s cancerous cells were mutated by a company’s drug is complicated. Glaxo’s decisions suggest it never wanted to consider that possibility. The clues were there. The documents show that Glaxo preferred not to find them.

Plaintiffs’ lawyer: *At any time when Zantac had been on the market for almost 50 years, did Glaxo cause anyone to test for the presence of NDMA, a probable human carcinogen, in the product it was selling to American consumers known as Zantac?*

Glaxo senior medical adviser: *Not to my knowledge.*

—Deposition, June 2021

NDMA, which is short for N-Nitrosodimethylamine, is a yellow liquid that dissolves in water. It doesn’t have an odor or much of a taste. It was first linked to cancer in 1956 and is most toxic to the liver. It’s one of a group of chemicals called nitrosamines, which by the 1970s were considered the most potent carcinogens yet discovered. They caused cancer in every species of animal tested. A single dose of less than a milligram of NDMA can mutate mice cells and stimulate tumors, and 2 grams can kill a person in days.

William Lijinsky was working as a cancer researcher for the US government in 1969 when he determined that nitrosamines could form in the stomach. Nitrites, a common chemical found in cured and grilled meat and in beer and coffee and vegetables, could combine with another group of chemicals called amines, compounds found in many medications. Acid in the stomach created the ideal environment for the reaction. The amount of nitrosamine created at one time might be insubstantial but over time could be dangerous. Lijinsky published studies about nitrosamines. He testified before Congress. He thought the easiest way to minimize the problem was to limit how much sodium nitrite food manufacturers could add to preserve and flavor meat. Ham, bacon, pastrami, corned beef, sausage: foods that, it turns out, are common causes of heartburn and acid reflux.

He also evaluated different amines, several hundred in all, to see which among them could form nitrosamines in simulated gastric conditions. They all could. Ranitidine didn’t exist yet, but it too includes an amine structure. Lijinksy’s research led in 1979 to an antihistamine commonly used as a sedative being taken off themarket because of its potential to cause cancer.

Rosalie Lijinsky, a genetic toxicologist who recently retired from the FDA, studied nitrosamines with her husband. “He thought they were the most important carcinogen,” she says. But he lost federal funding for his research—largely, she says, because of pressure from the food and pharmaceutical industries. He died in 2004 after suffering a stroke, thinking his work hadn’t been useful.

It seems to me that the regulatory agencies have been less than eager to act in the matter of nitrites and nitrosamines. There has been ample information available, if they had sought it. There is, of course, immense opposition by the manufacturing companies to any change.

—William Lijinsky, congressional testimony, 1977

In November 1980, a prominent pharmaceutical analyst at a well-known British investment firm sent investors a report titled “Glaxo, Ranitidine—Cause for Concern.” Glaxo was preparing to seek approval from the FDA to sell ranitidine in the US. The analyst wrote that academic research in the US suggested that, under certain conditions in the ▶

Scientists test Zantac at Valisure, which alerted the FDA to concerns in 2019

◀ stomach, ranitidine could form a potentially dangerous compound. The conditions were the chemical reaction that Lijinsky and others had described; the product, a chemical that might cause cancer. And the concern: the possible impact on sales. The analyst warned that until the debate about ranitidine's link to cancer was resolved, general practitioners in the US might be reluctant to prescribe the drug.

After the analyst's report came out, Glaxo's head of public relations, Geoff Potter, cautioned against overreacting. He wrote a memo to Paul Girolami, the CEO, who wasn't yet Sir Paul; the chairman of the board, Austin Bide, who was already Sir Austin; and other board members. In it Potter promised: "We will be watching the situation very closely with a view to proposing rapid defensive action should the position deteriorate." Later, in a deposition, the executive who was then Glaxo's associate director of clinical research would say that the board never asked him to test ranitidine to see if it might form a nitrosamine compound.

James Goetz's case will be the first to go to trial in a state court

In one trial in Britain during the summer of 1981, 11 healthy men were given 150mg of ranitidine twice a day, in the morning and evening, for four weeks. Glaxo scientists were looking to see if long-term use of ranitidine could affect gastric bacteria, specifically bacteria that could create more nitrite, which could allow nitrosamines to form. They found that it could. And they concluded the importance of that wasn't clear. In a summary later reviewed by the FDA, Glaxo scientists wrote that yes, high levels of nitrite could form nitrosamines, almost all of which are carcinogens. But the animal studies conducted so far hadn't shown that ranitidine was carcinogenic, so the level of human risk couldn't be estimated. Also, patients weren't meant to take the drug for long. "Ranitidine is recommended only for short-term use," the scientists concluded, "and carcinogenic risk, if any, should thus be minimized."

Many people would end up taking Zantac for months, sometimes years, even decades.

In October 1981, Glaxo announced plans to build a factory in North Carolina that could produce Zantac. The drug was already being sold in Britain and Italy. Researchers were studying it. Silvio De Flora, of the University of Genoa, published his results in the British medical journal the *Lancet* showing that when ranitidine was mixed with nitrite, the result was "toxic and mutagenic effects." De Flora didn't try to figure out the cause of the toxicity; he would later suggest that anyone prescribed Zantac limit their consumption of nitrite and take the drug well before or after a meal. Around the globe, instructions for taking Zantac to prevent heartburn would recommend using it close to mealtime.

Glaxo executives promptly got in touch with De Flora. "They tried to convince us of the safety of ranitidine," he said by email. "Pharmaceutical companies do not like this kind of study."

Five Glaxo scientists published a letter in the *Lancet* two weeks later to, they said, put De Flora's findings in perspective. They noted that De Flora had used concentrations of nitrite that would never be found in the human stomach. This would become Glaxo's standard argument. De Flora says researchers commonly use high doses of test compounds in lab experiments "because they evaluate a given effect in a short time as compared to the more common situation of being exposed to low doses for long periods of time."

In March 1982, Glaxo learned of another study revealing the potential dangers of ranitidine. The report, just a few pages long, was sent to the company by its rival, Smith, Kline & French, maker of Tagamet. Researchers there had also combined ranitidine with different concentrations of nitrite and had also observed the formation of a poison. They named it for Glaxo: NDMA.

Skepticism at Glaxo would be natural. A company had tested a competing product and found a flaw. Glaxo asked one of its scientists to conduct his own tests: Richard Tanner, who worked in the biochemical pharmacology division. He got the same results. He identified as much as

PHOTOGRAPH BY JESSICA PONS FOR BLOOMBERG BUSINESSWEEK

LESS THAN A MILLIGRAM OF NDMA CAN MUTATE MICE CELLS. TWO GRAMS CAN KILL A PERSON IN DAYS

232,000 nanograms of NDMA in some samples. When the FDA later deemed that a tiny amount of NDMA was acceptable in any drug, that amount was 96ng. Tanner didn't find NDMA when he used a lower nitrite level, which the company now says is closer to conditions in an actual human stomach. But back in 1982, court documents show, Glaxo kept the study secret. The associate director of clinical research in the US was never told about the Tanner report. The senior medical adviser for gastrointestinal research was unaware of it. So was the FDA.

Glaxo also knew of another potentially serious problem with ranitidine. It wasn't always stable. The drug was sensitive to heat and humidity, and when exposed to too much of either could degrade. This is what the FDA would later focus on: that in certain conditions, not necessarily extreme ones, sometimes normal room temperature, ranitidine starts to fall apart. That creates conditions for NDMA to form in the drug itself.

One exchange at the company in 1982 focused on preventing degradation of injectable ranitidine. Glaxo had just filed its application to sell ranitidine tablets and would soon seek approval for injections. John Padfield, the head of pharmaceutical development, had insisted that this version of ranitidine had to be kept chilled, at 4C (39F), as it was shipped from Britain, transported around the US and stored at regional warehouses. Not doing so, he wrote in March, would be "a very dangerous thing." A few months later, in a July memo, company executives wrote: "Refrigeration of the injection would not be acceptable to Glaxo marketing." Padfield was adamant. "The product is very sensitive to temperature," he wrote back. "It is imperative that the product is protected in the way we have discussed."

Things had moved rapidly in North Carolina. The first human trials of ranitidine in the US had begun only two years before Glaxo filed its new drug application in March 1982. But Fred Eshelman, who was the associate director of clinical research then, says the company was small and the staff young, they didn't ever compromise safety, and they didn't have to deal with a lot of bureaucracy. "Everybody thought it was a great drug," he says. "The quicker we could get it to market, the quicker patients could use it. We were all devoted to good things." Eshelman was among the many who should have seen the Tanner study but didn't. He doesn't want to comment on that now, but says: "If this drug were toxic in and of itself, we would have found out long ago."

Plaintiffs' lawyer: *It is completely unheard of in the industry to go that fast.*

Fred Eshelman: *Yes, sir.*

Lawyer: *So, would it be fair to say that the clinical development of ranitidine was done quickly at a frenetic pace that took a lot of work?*

Eshelman: *Fair enough.*

—Deposition, May 2021

In May 1982, Eshelman and a group of Glaxo scientists gathered in a room at the National Library of Medicine to present the case for Zantac to a panel of independent researchers and a group of FDA officials. The panel would recommend whether the FDA should approve the drug for sale in the US.

David Jack, who had helped discover ranitidine, spoke first. He noted that the company had carried out extensive toxicological studies on ranitidine and found nothing concerning. But that morning, he said, "we want to focus only on the part which raises the real problem in some people's mind, namely the possibility of carcinogenesis with drugs of this kind." He and other Glaxo scientists presented three studies that showed long-term use of ranitidine (over about two years) didn't cause cancer in rats or mice. "Ranitidine proved to be a singularly nontoxic compound," one of Jack's colleagues said. "No evidence of ranitidine being itself carcinogenic either in the stomach or for that matter anywhere else."

The Glaxo scientists disputed the idea that ranitidine could form a nitrosamine under any normal human conditions. They didn't mention the company's Tanner study. Richard Klein, who worked at the FDA for more than 40 years, including with drug approval teams (though not Zantac's), says that had the agency known about the Tanner study, it might have at least "inspired the FDA to ask more questions, to ask for more data. It might have raised FDA's suspicion."

As it was, the discussion moved past any concerns about cancer to specific dosing and the type of ulcers Zantac would treat. There wasn't much talk of how the drug needed to be transported and stored and what warnings, if any, should be on the label. The pace was brisk. Right before their lunch break, the outside experts voted to recommend the FDA approve the medication: 150mg twice a day for up to eight weeks to treat acute duodenal ulcers, the most common kind. The label would ultimately include instructions to store the pills at home in a dry place that didn't exceed 86F. A year later, in May 1983, the FDA granted Glaxo approval to sell Zantac. The *New York Times* wrote that the drug, which was already sold in 31 countries, was "several times more powerful than Tagamet and said to have fewer side effects, ▶

◀ though both drugs are considered so safe that physicians have prescribed them for a far wider range of gastric complaints than the companies have suggested."

Zantac's sales in the US that first year were about $125 million, which made it one of the best launches of a drug ever. "Fred Eshelman was the hero at Glaxo because of Zantac," says Joe Graedon, a North Carolina pharmacologist who co-founded the People's Pharmacy, a consumer health organization. "The head of Glaxo said, 'Zantac is the engine that pulls the train.' It was the moneymaker, the giant killer." Eshelman would go on to start his own firm, which conducted new drug trials for pharmaceutical companies. Several Glaxo executives would join him. He sold the business in 2011 for $3.9 billion and later donated $100 million to the pharmacy school at the University of North Carolina at Chapel Hill. It was already named after him.

It's safe. It works. The end.
—A plaque in Fred Eshelman's Glaxo office commemorating Zantac's approval

Glaxo's marketing campaign was a masterful effort to undermine Tagamet, then the world's bestselling prescription drug. Executives knew Zantac had more active ingredient in each pill than Tagamet did, so they marketed it as more effective. They knew that patients would be prescribed Zantac twice a day instead of four times. They emphasized to doctors that Zantac was more convenient. They knew some, not many, patients had suffered side effects with Tagamet—bad drug interactions, mental confusion. They marketed Zantac as safer. And Glaxo priced Zantac higher, some 15% to 25% higher, as evidence that it was superior to Tagamet. Smith, Kline & French responded with its own campaign for Tagamet, calling itself the ulcer expert.

Glaxo tripled its sales force by working with the Swiss drug company Hoffmann-La Roche, which at the time had a big staff but no big drug. They started marketing Zantac to gastroenterologists, as expected, then less expectedly began holding "educational symposia" for primary-care physicians, osteopaths and pharmacists.

Three years after Zantac was introduced in the US, the FDA reprimanded Glaxo for repeatedly making false promotional claims, most recently as it sought to become eligible for government reimbursement programs. "We apparently have had little success in achieving voluntary correction of these advertising and promotional practices on the part of your firm," the FDA wrote in a four-page letter in May 1986. It concluded with the threat of regulatory action. Glaxo replied that the agency had misinterpreted its actions.

That year, Tagamet became the first billion-dollar drug. The next year, Zantac overtook Tagamet.

In March 1988, Glaxo commissioned a Gallup Poll titled "Heartburn Across America." It found 44% of the adult population suffered heartburn monthly. Zantac could be prescribed for heartburn by then, but plenty of antacids were available that didn't require a prescription. Glaxo promoted the survey on television and in print. The ads noted that heartburn and other symptoms of chronic reflux could signal diseases such as ulcers and suggested seeing a physician.

A respected gastroenterologist in North Carolina conducted a study in the winter of 1988 that showed Zantac could help reduce heartburn in runners: a new group of potential patients with a newly named problem, runners' reflux. The study was small and never peer-reviewed, but the doctor's prominence—and Glaxo's public-relations agency—assured it received attention. The *New York Times* later reported that the doctor was a paid consultant to Glaxo. He said he didn't think Glaxo would capitalize on the study.

By 1989, Zantac was worth $2 billion. It accounted for half of Glaxo's sales and 53% of the market for prescription ulcer remedies.

In 1993 the FDA followed through on its threats regarding the marketing of Zantac. The agency said in a warning letter that Glaxo had undertaken a "repetitive course of conduct" to disseminate misleading information about Zantac being superior to Tagamet in advertising and promotions. The agency demanded that Glaxo write to US doctors and publish advertisements in 12 leading medical journals to correct any such statements. "Most firms don't make mistakes in promotional material," an FDA spokesman told London's *Sunday Times*. "This is a worst-case scenario." Two months later, Glaxo released its "corrective advertising" campaign.

Glaxo had lots of reasons to cooperate with the FDA. Among them was that it was working on developing lower-dose, over-the-counter versions of Zantac meant to treat heartburn. The FDA would have to approve. One of the other changes executives were considering for the new tablets was their color. During some stability tests, the tablets, which were white, were turning yellow and brown. Glaxo wanted to mask that. They settled on a pink coating, made of iron oxide, for the new pills. Discoloration is often a sign that tablets are degrading. In some cases, degradation can cause dangerous impurities to form. Glaxo said that wasn't the case with Zantac. "Color was used in the coat in order to ensure a uniform appearance of the tablets throughout their shelf life," Ian Winterborn, who was working on developing the over-the-counter version, said in a deposition. "There was no concern about degradation associated with the color change."

When Glaxo completed its application for over-the-counter

GSK FINALLY HANDED OVER THE REPORT, WHICH HAD BEEN TUCKED AWAY SINCE 1982

Zantac, Winterborn was one of many recipients of a congratulatory email. "This concludes what I believe to be a heroic effort from everyone involved in this project over the past two and a half years," an executive wrote in late 1994. "I believe this to be one of the most significant accomplishments at Glaxo of all time."

In the spring of 1996, Glaxo celebrated the introduction of the Zantac 75mg over-the-counter pill. It was pink and could be taken once or twice a day. Americans were already spending about a billion dollars every year for heartburn relief. Glaxo's marketers were ready. Their catchphrase: "The Legend Lives On."

There was nothing in Zantac's elements that made it a billion-dollar drug. We made it that product.
—Paul Girolami, chairman of the Glaxo board, in the *Financial Times,* 1988

In 1995, Glaxo completed a hostile takeover of another British drug company, Wellcome. Five years later, in 2000, Glaxo Wellcome acquired its longtime rival, known then as SmithKline Beecham. It was the biggest merger in the industry's history and created the biggest drug company in the world, GlaxoSmithKline.

By then James Goetz, an aviation engineer who lives in Southern California, had been taking Zantac for years: first prescription, then over-the-counter. After the FDA approved generic versions, he took those, too. John Russell, who lives near Los Angeles, was diagnosed with gastritis and started taking the medication in 2001, picking it up from local gas stations and drugstores.

Issues with discoloration of Zantac persisted. In 2010, Andrew Searle, who oversaw genotoxic risk assessments at GSK, was asked to probe why injectable versions of Zantac were turning yellow. Searle's investigation tested for impurities that were known to cause such yellow discoloration. NDMA used in labs is yellow, but he didn't test for it. The issue came up again in 2015 when a manufacturing site in China reported problems with discolored and degraded Zantac tablets. GSK sent doctors a letter stating that the company hadn't been able to identify any specific impurities but couldn't confirm that the brown discolored tablets met its safety standards. No one looked for NDMA. In a deposition, Searle blamed the issue on inappropriate storage.

Between those two incidents were two others, unrelated to Zantac, that created unwanted scrutiny for GSK. In 2012 the company agreed to plead guilty and pay a $3 billion fine for marketing drugs for inappropriate uses, disregarding safety data and cheating Medicaid. The drugs were among the company's most popular after Zantac: Paxil, Wellbutrin and the diabetes drug Avandia. The US Department of Justice called it the largest health-care fraud settlement in US history and the largest payment ever by a drug company. Two years later, China fined GSK $500 million and deported a top executive for bribing doctors to prescribe its drugs. The company told the BBC it had "published a statement of apology to the Chinese government and its people."

Plaintiffs' lawyer: *Was it known that ranitidine would degrade under conditions of high temperature?*

Andy Whitehead, director of second-generation research and development: *It would have been known in the '80s as part of the development.*

Lawyer: *And when was it known that ranitidine would degrade when subjected to moisture?*

Whitehead: *That would have been part of the original development work.*

Lawyer: *So that ranitidine could degrade under conditions of high temperature and moisture has been known for almost 40 years?*

Whitehead: *That's correct because of the hydrolytic pathway that was investigated as part of the development.*
—Deposition, May 2022

Goetz was 60 in 2017 when he was diagnosed with bladder cancer. That in and of itself wasn't too unusual; 60 is about the age this particular cancer is often diagnosed in men. Smokers get bladder cancer, but Goetz hadn't smoked since he was 22. His job hadn't exposed him to any potentially harmful chemicals. It was perplexing, but he had no reason to think his getting cancer was anything other than random. Unfortunate, terrifying, but random. His doctor scraped out the tumors and treated him with immunotherapy. Then they waited. Chances were the cancer would come back, and when it did it was aggressive. The doctor had to remove Goetz's bladder and prostate and 20 feet of his intestines. Afterward, he suffered kidney stones and sepsis. Goetz will be the first of thousands to go to trial against GSK. Because of that, his lawyers declined to allow him to comment for this story.

In September 2019 the FDA received a 19-page document that made some alarming claims about ranitidine. Valisure, a private lab operating independently of the FDA, said it had found extremely high levels of NDMA in Zantac and several generic versions of ranitidine. Valisure had begun testing for NDMA the year before, when the FDA first recalled batches of the blood pressure medication valsartan because they were contaminated with it. This situation seemed worse. Valisure had found NDMA in every version of ranitidine it tested and concluded the problem was inherent to the molecule itself.

The FDA issued an alert but also questioned the testing method Valisure used. The agency said it would conduct its own tests with its own protocols. Within a month, at least two dozen countries pulled ranitidine from stores or halted its distribution. GSK, which by then had sold the rights to sell Zantac in the US, acted on its own to stop the supply of the drug. So did Sanofi, the French company that acquired the US rights in 2017 from Boehringer Ingelheim GmbH, and Pfizer, which had sold Zantac from 1998 to 2006.

"All, we have an urgent need to identify if the following ▶

◀ study report was submitted in the European Union and United States," a senior GSK executive wrote colleagues that November. She was talking about the Tanner report, and the answer was no, it hadn't been submitted as part of any new drug application. GSK then, finally, handed over the report, which had been tucked away since 1982.

The FDA made a rare and drastic decision in April 2020: It forced the makers of ranitidine—any version, any dose—to stop producing and selling the drug altogether. Ranitidine was finished. "NDMA levels increase in ranitidine even under normal storage conditions," the agency said. "And NDMA has been found to increase significantly in samples stored at higher temperatures, including temperatures the product may be exposed to during distribution and handling by consumers." Graedon, of the People's Pharmacy, calls this "the first example we have where storage conditions can have a profound impact on the quality of medicine, and the FDA has admitted that."

It wasn't until October 2021 that the FDA shared some specifics about what the agency had detected, and then it did so not in a published paper but during a monthly lecture series called FDA Grand Rounds. One tablet of a cool mint version of ranitidine, the agency said, contained 357ng of NDMA when it was initially tested—almost four times the FDA's limit in any drug—and 931ng five months later.

The FDA declined to comment on any of its interactions with Glaxo but said in a statement that it works to provide access to safe, effective and quality-made drugs, evaluating the benefits and risks "according to the science of the day"; that it requests the removal of a drug from the market when appropriate; and that "when new impurities are identified, new manufacturing processes used or when the science advances, the FDA works to improve the safety, quality and effectiveness and will continue to investigate emerging risks to patients' health." The FDA's decision to force ranitidine off the market was based on how NDMA forms in the drug, not the stomach. The agency says that once ingested, ranitidine doesn't cause more NDMA to form. Some scientists disagree.

In December 2020, GSK published the results of what's called a root cause analysis. It was inconclusive: The company's scientists couldn't determine exactly how the NDMA was forming in ranitidine and noted that back in the 1970s, when the drug was first developed, no one could have reasonably predicted that NDMA would ever form.

A year and a half later, the FDA made another rare and consequential decision. Even though it had found NDMA in ranitidine and even though ranitidine is a probable human carcinogen, the agency said there were "no consistent signals" that Zantac increases cancer risk. It did so on page 8 of a 10-page study examining NDMA levels in the urine of people who took ranitidine. The statement relied on seven papers by outside scientists. One showed a link between ranitidine and breast cancer, but the agency criticized its methods. A second raised concerns about liver cancer, though the authors said they didn't yet have enough data to confirm a link. It didn't seem as if the FDA's was the final word, but the statement is now a regular part of Glaxo's public-relations and, presumably, legal defense. "Guiltless by association" is what some scientists call this. Three studies since then have found a link between the drug and cancer, most notably bladder and liver cancers. The FDA says it stands by its statement, which critics say does also absolve the agency for allowing a dangerous chemical to lurk in a drug for decades.

> *"I just wish I had a better memory of all the issues and studies that were done when we were developing Zantac. There were concerns about nitrosamines at the time, and I know that there were lifetime carcinogenicity studies undertaken."*
> —Ian Winterborn, in an email read during a deposition, May 2022

After a while, the over-the-counter Zantac pills John Russell was taking weren't strong enough to ease his discomfort, and in 2017 a doctor prescribed a daily 300mg dose. A year and a half later, Russell noticed blood in his urine. A doctor found a 3-centimeter tumor in his bladder. Russell, like Goetz, was told the cancer would likely return, and it did. "It's like a weed," he says. His primary-care physician was baffled, Russell says. "I never smoked—that's the highest risk factor—I've never worked around chemicals or plastics. I have no hereditary connection. I had barely heard of bladder cancer." Every cystoscopy Russell has had since 2021 has revealed a tumor; he's had four surgeries in the past 18 months.

When he learned of Zantac's recall, he thought: "I've taken thousands of those pills." Russell played college football; working out used to be his hobby. But now, at 58, he's weakened from the surgeries and the worry. "I want the perpetrator," he says. Russell read about the federal judge's decision in December. "I would like to have my day in court," he says. "I would like a judge to tell me where they think my cancer came from."

James Goetz's kidneys are failing and soon he'll need dialysis, but he's able to work and expects to testify in the courtroom in Alameda County. When Zantac was recalled, he kept four bottles he'd already purchased. They're in the freezer in the office of one of his attorneys, Brent Wisner, as are leftover pills from Russell. Tests showed that one of Goetz's pills is contaminated with 3,000ng of NDMA, Wisner says; one of Russell's has more than twice as much. Wisner says he's invited GSK to test the tablets, but the company hasn't done so.

Boehringer, Pfizer and Sanofi settled Goetz's case in December; the amount of the settlement is being kept secret. GSK could settle, too. If it doesn't, Wisner and his partner in the case, Jennifer Moore, will be trying it in the same court where Wisner won a $2 billion verdict against Bayer AG on behalf of a couple who claimed the herbicide Roundup had caused their cancers. A judge later reduced the verdict to $87 million.

Moore also secured large verdicts for clients in the Roundup litigation. She says that with the weedkiller there wasn't scientific consensus over whether it was carcinogenic, while NDMA is acknowledged to be dangerous. "Here we have every scientific organization, every regulatory agency,

all saying NDMA is a carcinogen in humans," she says. "And here we have our own client's pill showing there is a carcinogen at astronomical levels."

The Goetz trial has particular significance as the first after the federal ruling in Florida. There was a sense then, at the company and among investors, that the danger had passed. "Obviously, we were delighted with the outcome," GSK's chief executive, Emma Walmsley, said on a Feb. 1 earnings call.

In GSK's telling, Rosenberg's review of 13 epidemiological studies found no connection between ranitidine and any cancer. But that's not quite right: She reviewed 11 studies, and four of them found an association that the scientists said merited further research. Many of the studies Rosenberg evaluated had examined overall cancer risk. Wisner says an analysis combining epidemiological studies that contain bladder cancer data, including some considered by Rosenberg, shows "a statistically significant elevated risk if you take ranitidine."

It's fair to say that the science is unsettled. And it's likely that different judges—and juries—will come to different conclusions. GSK could face years of lawsuits in California, Delaware and other states, with the possibility of billions in damages. Estimates range from $3.5 billion to $17 billion. The company also disclosed in July 2020 that it was cooperating with a Justice Department probe related to Zantac.

Pfizer and Sanofi face similar legal claims about selling a potentially dangerous product. Like GSK, they dispute that Zantac poses any health threat. When asked for comment, Pfizer referred to a statement on its website that notes that the company last sold Zantac in 2006 and that it "has significant defenses to this litigation and there are significant legal and factual issues that remain to be addressed by the courts." A Sanofi spokesperson says: "Sanofi remains confident in our defenses across this litigation given the clear lack of scientific support for plaintiffs' claims."

Sanofi conducted its own investigation into how NDMA formed in Zantac tablets, hoping that would allow it to make some changes that would withstand FDA scrutiny and bring the drug back to the market. The company called the effort Project Churchill. It yielded an unwanted result, which led to an unprecedented decision. Sanofi couldn't find an acceptable way to make Zantac with the ingredient that defined it as Zantac, ranitidine.

Instead, in 2021 the company reformulated Zantac with famotidine, the active ingredient that has defined another heartburn drug, Pepcid. The new Zantac is in stores now. On its website, Sanofi describes this version of the drug as "building on the Zantac brand's established history and legacy."

"Wait a minute, you're telling me that they are marketing OTC famotidine and calling it Zantac? I'm obviously dumbfounded. I don't know what to make of that."
—Fred Eshelman in a deposition, May 2021 B