



How Merck made a killing

BY JIM GILES

Stockmarket pressure to find “blockbuster” drugs has forced drug companies to push products to market ever more aggressively. In the case of Merck’s painkiller Vioxx, this had disastrous and lethal results. This is the story of how a blockbuster backfired

There are two remarkable things about the painkiller Vioxx. One was its disastrous impact on those who took it. Before it was pulled from the market in September 2004, Vioxx probably did more harm than any other modern prescription medicine. Critics of the drug have estimated that up to 140,000 Americans suffered heart attacks or strokes and about a third died as a result of taking it—and that is not counting those who died in the other countries where the drug was sold. It was as if a full jumbo jet dropped from the sky every week for five years, yet no one noticed.

The other notable aspect of Vioxx followed its withdrawal. Big pharma does not like to go to court, in part because liability trials can involve public washing of dirty corporate linen. But when the vic-

tims of Vioxx started legal action, Merck, the drug’s manufacturers, decided *not* to settle privately. As a result, the company’s internal deliberations over Vioxx—the emails, memos, reports—have been made public. For anyone who ever visits a doctor, these documents matter. There are 20m pages of them. They constitute a warts-and-all record of what Merck’s staff were telling each other—but not necessarily anyone else—about Vioxx. It’s all there: bad tempers, bad spelling, back-slapping, back-stabbing. We trust drugs companies to be able to do things: look objectively at data, make decisions about people’s safety, gauge what patients need to know in order to stay alive. The documents show that this self-regulation can simply dissolve when big profits are at stake.

THE BIG BLOCKBUSTER GAME

The pharmaceutical business is highly lucrative. Johnson & Johnson, one of the sector’s biggest companies, exceeded \$60bn in sales and \$11bn in net profit in 2007—a margin of 17 per cent, close to the industry average. Only two other types of businesses—telecommunication equipment suppliers and oil companies—have higher margins. And people at the top are well rewarded. William Weldon, Johnson & Johnson’s CEO, is likely to earn over \$16m in 2008.

Yet these profits are fragile. Lipitor, the world’s bestselling cholesterol medication, generates over \$10bn in sales a year. That is good news for Pfizer, the company that makes it. But Pfizer’s total revenue in 2007 was just under \$50bn; this single blockbuster product (a “blockbuster” is a drug with annual sales of \$1bn or more) accounted for a fifth of its revenues and much more of its profits. In March 2010, the US patent on Lipitor will expire and cheaper versions will appear. Pfizer, like its competitors, is under constant pressure to find its next blockbuster drug.

This pressure has grown as the industry has changed. Over the past 25 years, it has consolidated into five megaliths, each with sales of over \$20bn a year. Most need to have several blockbusters to maintain their place in the pecking order. And as big pharma has chased more blockbusters, it has become more scandal-prone. Between 1977 and 1996, there were nine products withdrawn from the US market, according to Aon Risk Services. From 1997 to 2007, the number jumped to 15. GlaxoSmithKline has been accused of obscuring the link between suicide risk and the anti-depressant Seroxat; Eli Lilly’s critics say the company hid the diabetes cases caused by its best-selling schizophrenia drug, Zyprexa. (Both companies have denied any wrongdoing.) But it is seldom front-page news when a company is accused of obscuring

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the dangers of a drug, largely because most pharmaceutical scandals involve an allegation and an out-of-court settlement. Corporate leaks are rare, whistleblowers rarer. The documents that emerge often reveal individual misdeeds, but not a drug's full history. So it's hard to know if the companies' answers—an incorrect statistical analysis perhaps—are excuses or explanations. This was different with Vioxx.

“THANK YOU AND GOODBYE”

The story begins in 1991, when Daniel Simmons of Brigham Young University announced the discovery of an enzyme in the *Proceedings of the National Academy of Sciences*. The enzyme, known as COX-2, helps generate the pain signals that travel from the site of an injury to the brain. Drug companies were excited about the discovery because if they could find a substance that neutralised its effects, they might have the basis for a new kind of painkiller.

Merck, one of the industry's largest companies, quickly joined the race. By 1998 it had made good progress with Vioxx, its candidate drug. But it needed to convince the US Food and Drug Administration agency—the regulatory body that approves new drugs—that the product was safe and effective. To make its case, Merck supplied the FDA with a clutch of trials involving around 5,000 patients. But the company had focused on only one potential side effect: damage to stomach lining. None of the studies were designed to examine the risk of heart attacks.

That is not as careless as it sounds. One of the great difficulties of drug development is knowing what side effects to look for. There are anti-smoking drugs that make people depressed and allergy medications that trigger headaches. Stomach damage is the big drawback of painkillers such as ibuprofen, so Merck had every reason to focus on this. Yet even in the late 1990s, there were scientists who feared that the company studies had missed something big.

One was Garret FitzGerald of the University of Pennsylvania. He has spent three decades studying molecules that smooth the flow of the blood, and those that cause it to thicken and clot. In 1997, FitzGerald showed in a study (funded by Merck) that Vioxx interfered with a hormone that thins the blood and relaxes blood vessels. That worried him; less hormone could mean thicker blood and tighter veins and arteries, making patients susceptible to heart attacks and strokes. It was the first red flag for the drug.

FitzGerald took the results to Merck before publishing them. This led to an acrimonious discussion. FitzGerald had to fight off requests to tone down his conclusion and remove references to work by other researchers that supported his findings. Merck did follow up the findings, but FitzGerald was not invited to help. When he suggested that Merck and

a competitor examine the risks, he got the same answer from both: “Thank you and goodbye.”

THE CARROT AND STICK APPROACH

It is one thing to get a drug onto the market. But to sell Vioxx in large quantities, Merck needed to convince doctors that the drug was not only safe, but safer than the painkillers that they were already prescribing. In early 1999, Merck had begun a trial named Vigor. Over 8,000 arthritis sufferers took part. Half were given daily doses of Vioxx; the others received naproxen, an ibuprofen-like painkiller. By March of the following year, the results were in: Vioxx halved the risk of stomach damage.

Merck invested huge sums publicising the results, purchasing almost 1m reprints to give to doctors, and spending \$160m advertising the drug directly to American consumers (such advertising is banned in the EU). Dorothy Hamill, a former Olympic figure-skating gold medalist, appeared in adverts describing how Vioxx allowed her to overcome arthritis and continue to skate. Yet the Vigor results were not all positive. Among the 2,300 patients who took the drug, 20 heart attacks occurred. A small number but an important one—it was five times greater that the figure for naproxen. And for every patient that avoided stomach damage from naproxen, the new drug had the potential to cause a patient to get a blood clot—a much more dangerous side effect. This should have flagged up a warning that Vioxx caused potentially serious cardiovascular problems. Edward Scolnick, Merck's executive vice president for science and technology, appeared to realise this. In his email to colleagues in March 2000, he noted that the “CV events are clearly there” (CV stands for cardiovascular) and described that result as a “shame.” However, Merck did not properly share this data with doctors and patients.

The Vigor results were published in the *New England Journal of Medicine*, a respected and widely-read journal. But the reporting was selective. Three of the heart attacks attributed to Vioxx were missing, which bumped down the risk. (The researchers who ran the study later said that, for reasons that remain unclear, they had stopped counting heart attacks one month before ceasing to collect other data.) The blood clot numbers were not included. Merck supplied the full data to the FDA and later informed some doctors. But the journal article remained uncorrected until after Vioxx was withdrawn, so many physicians prescribed the drug without knowing that the data they saw was incomplete. The FDA said that the evidence on its own was not sufficient to warrant the removal of Vioxx. That's probably correct. But knowledge of the extra deaths and blood clots would surely have made doctors more cautious about prescribing the drug for

patients with a history of heart attacks, for example.

Even with three heart attacks and the blood clot data missing, the number of heart attacks on Vioxx was 17, compared with only four on naproxen, indicating that Vioxx was more dangerous than other painkillers. Some doctors noticed and chose to prescribe Celebrex instead, a rival COX-2 drug released by Pfizer shortly before Vioxx. Others spoke critically about Vioxx at medical education events. This threatened to blunt Merck's marketing campaign. So Merck had plans for these critics. An internal company list, probably compiled during 2000, details key arthritis and analgesia physicians and their attitudes towards Vioxx. Physicians who had not prescribed the drug, or had criticised it, were labelled "neutralised."

It's not clear precisely what was meant by this. The company says that some physicians had been making inaccurate statements about Vioxx and that Merck wanted to ensure these physicians took a more balanced, or "neutral," position. But the document also shows that doctors who had been reluctant to prescribe Vioxx were invited to speak at education events run by Merck. A typical fee might be \$2,000 per engagement, plus expenses. The company also provided one of the doctors on the list with \$25,000 for a clinical trial he was proposing.

For James MacMillen, a doctor based in Mechanicsburg, Pennsylvania, and a critic of Vioxx, Merck seems to have opted for the stick rather than the carrot. MacMillen is described in the document as a "loose cannon," loyal to Pfizer, the manufacturer of Celebrex. "Strong recommendation to discredit him," reads the document. The records do not reveal what happened to MacMillen, but there is a hint to his fate in a letter sent to Merck in early 2001 by James Fries, a professor of medicine at Stanford University. Fries complained that Merck staff were approaching the academic bosses of the critics and threatening to cut off the research funds Merck provided to their institutions. Fries mentioned that MacMillen believed he had lost a position at a local university due to such an intervention.

Most family doctors knew nothing of this intrigue. The average community physician in the US does not have time to read medical journals in detail. They rely much more on the visits of drug company sales representatives. Merck had assigned 3,000 US salespeople to Vioxx. They were coached on how to move the conversation from chat about sports or the weather onto healthcare and then Merck products. They were taught how to identify and focus on the physicians who appeared to be the "thought leader" in a department or hospital, and offer them speaking engagements, provided they delivered "favourable yet balanced" opinions on Vioxx. If a doctor asked about heart risks, the reps were told not to mention the

Vigor results. Instead, they brought out a pamphlet stating that patients on other painkillers were eight times more likely to die from heart attacks. The figure came from a series of small trials in which heart problems had not even been properly monitored. An FDA expert later described the pamphlet as "scientifically inappropriate" and "ridiculous." But that was not until 2005, when the drug had been withdrawn.

DODGE BALL VIOXX

By the end of 2000, the company's investment had paid off. In the US alone the drug had brought in about \$2bn—well into serious blockbuster territory. However, critics believe it also caused around 20,000 heart attacks and strokes, about a third of which were fatal. In early 2001, doctors were exchanging tales about heart problems among relatively young and healthy Vioxx users. That summer, an independent group of scientists would publish a paper in the *Journal of the American Medical Association*, suggesting that Vioxx more than doubled the risk of patients developing a heart problem. Meanwhile, Merck was stepping up its efforts to sell the drug.

To help train new sales reps, Merck used a card game called "Dodge Ball Vioxx." Each card listed an "obstacle": a question a doctor might ask about the safety or effectiveness of Vioxx. If they asked about the cardiovascular risks of the drug, reps were told to say that some Vioxx patients might need to take aspirin, a drug that protects the heart. Not a lie, but not a direct answer either. An effective dodge.

But out in the field it was getting harder for reps to keep dodging questions. In February 2001, a panel of FDA advisors met at the agency's headquarters in Rockville, Maryland. They looked at the Vigor data and results from two further, but then unpublished, studies of Vioxx. They concluded that clinicians be warned of the heart risks identified in Vigor.

Soon after, Merck launched "Project A&A XXceleration." It was designed to boost Vioxx sales in the two "A's," arthritis and analgesia. Reps were told to target 50 doctors deemed "high volume" prescribers. In April 2001, Merck executive Jo Jerman discussed progress in a voicemail message to reps. Market share in arthritis and analgesia was up 17 per cent. "Woo doggie!" she said. "That is exciting." She added that the "only thing left is to put Project A&A XXceleration into overdrive... if you hit those 2-4 share point increases, you'll be rewarded handsomely... Go get em guys, good luck and great selling!" Great selling, indeed: 2001 was another \$2bn plus year for Vioxx.

THE CASE OF PATIENT 5005

Next time you open a packet of prescription drugs, look at the foldout information sheet it comes with. For drug companies, every word on that sheet has a

potential impact on sales. Every benefit that is noted and every risk that is not will make doctors more likely to prescribe that drug. During 2001, Merck was pushing hard to have the Vioxx label changed. Since the first version had been approved, the Vigor results had showed that Vioxx caused less stomach damage. This was Merck's key selling point and it badly wanted it on the label. It was equally important that the heart risk not be mentioned.

Unfortunately for Merck, the company's own scientists were producing unhelpful data. During the first half of 2001, they had been running Protocol 906, a 450-patient trial that compared Vioxx with rival Celebrex. The results showed that Vioxx scored no better as a pain reliever, but caused more of some types of side effects. Eight people taking the drug reported minor cardiovascular problems, compared with two on Celebrex. Merck scientist Andreas Moan received the results on 23rd July and emailed colleagues the same day: "this is a very serious result and you will hardly be surprised at the idea of keeping this VERY TIGHT for the moment."

Merck did just that. Earlier that month, the FDA had asked the company for an update on Vioxx. Merck replied a week after Moan sent his message, but did not include all the results from protocol 906. The update noted that Celebrex caused a small number of serious side effects and attributed only minor effects, such as headaches and diarrhoea, to Vioxx. There was no mention of the cardiovascular results.

Merck's update also contained news of patient 5005. This was a 73-year-old woman who had died in October 1999 during another trial, named Advantage. An FDA scientist named Maria Lourdes Villalba was part of the team that examined the data. The cause of patient 5005's death was listed as unknown. But the woman had called her son shortly before complaining of chest pain. In Villalba's opinion, that meant a heart attack was the most likely cause. This single fatality was important. Three other patients on Vioxx had died of heart problems during Advantage, compared to zero in the naproxen group. If the number of Vioxx deaths had been recorded as four, then the difference between the Vioxx and naproxen groups would have passed the test of "statistical significance," say doctors who testified on behalf of Vioxx victims. As it was, it did not.

What Villalba did not know was Merck scientists had debated how to classify patient 5005 in November 2000. Eliav Barr, the scientist charged with deciding, said that a heart attack was the most likely explanation. "If it is easier to call this an unknown cause of death, I could be persuaded to say that as well," he added in an email to a senior scientist. His superior replied: "I would prefer unknown cause of death so that we don't raise concerns." (Merck say

that the "concern" was that the company would be asked why it had not identified the death as a heart attack immediately after it occurred.)

The Advantage results especially infuriated Merck executive vice president Scolnick. He had never wanted the trial to go ahead. When the FDA asked for the Advantage data, Scolnick told a colleague he feared an "intellectually redundant" study would compromise efforts to get "the labelling we had wanted." That's because Advantage was not actually a true clinical trial but a promotional exercise, designed and run by a group affiliated with Merck's marketing team and independent of Scolnick's research labs. Industry insiders call such trails "seeding trials." They are widely considered unethical, as patients and doctors are misled and exposed to unnecessary risk.

A few months later, Scolnick's fears were realised. The FDA sent its proposed label on 15th October. It included the Advantage results and mentioned the cardiovascular risks. "Be assured that we will not accept this label," he wrote that evening in an email. "We knew it would be UGLY and it is," replied a colleague. Scolnick answered just after midnight: "It is ugly cubed. They are bastards."

A STEP TOO FAR

By the end of 2001 Vioxx was Merck's second biggest seller and the patent had 12 years to run. It was the kind of product that makes drug companies highly profitable, and allows them to reward senior employees so well. Scolnick earned \$1.6m in pay and bonuses that year; Raymond Gilmartin, Merck's CEO, took home \$2.9m. But both knew that Vioxx could earn the company even more money if it could be prescribed for a wider range of ailments. It was this restless search for new treatments that was ultimately to lead to Vioxx's withdrawal.

On the evening of 23rd September 2004, John



Baron, a professor at Dartmouth Medical School in New Hampshire, called Merck. Baron was investigating whether Vioxx could be used to treat benign tumours that cause colon cancer. That week, his colleagues had updated him on a trial he had helped establish. The results were alarming. Vioxx was causing so many heart problems that Baron was calling to say that the study had to be stopped.

To suspend a study is to admit, incontrovertibly, that something is wrong. Gilmartin, Merck's CEO, spent the weekend digesting the data and wondering what to do next. The trial showed that patients on Vioxx developed blood clots at twice the rate of those given a placebo. It was one damning piece of evidence too many. On the Tuesday after the weekend, Gilmartin met with Merck's board. Two days later, they announced that Vioxx was being withdrawn.

The immediate impact on Merck was devastating. It cost around \$700m just to recall the drug. The stock price almost halved in under two months. The US department of justice launched an investigation. Gilmartin stood down in May, one year early. By December 2005, over 19,000 people in the US had filed claims for compensation. Tens of thousands were to come. Merck shareholders launched legal actions demanding compensation for lost earnings. Some analysts predicted Vioxx would cost the company \$30bn; enough, perhaps, to put it out of business.

Most big drug companies have had to deal with litigation—if not quite on this scale. Most negotiate in private to keep legal bills down and prevent disclosures. But Merck chose to fight every case, claiming it had done nothing wrong. Legal experts suggest a different reason: that the company knew it had a good enough defence to triumph in at least a few cases, and to draw out the process with appeals to those it lost. The costs would mount for the plaintiffs, making them more likely to opt for a smaller settlement.

Initially, this looked like a miscalculation. The first case, brought by the widow of 59-year-old Robert Ernst, who died after taking Vioxx for eight months, was heard in Texas in July 2005. The company was up against Mark Lanier, a superb lawyer with a folksy manner and political ambitions. Lanier's team worked the mountain of internal Merck documents to great effect. The jury heard about dodge ball and what Lanier castigated as deceptive data. Merck's lawyers fired insensitive questions at the victim's widow. In the end, the jury decided that Merck should have warned of the dangers of Vioxx. The award to the widow was \$253m.

Three years later, however, Merck's decision appears to have been a brilliant gamble. Twelve of the next 17 juries ruled in Merck's favour. The problem for the plaintiffs is that there is never an unambiguous link between Vioxx and a patient's heart attack. Vioxx

tightens blood vessels and makes the blood prone to clot, both of which make heart attacks more likely. But these symptoms may have occurred anyway; heart attacks are the most common cause of death amongst the elderly population. At the epidemiological level, the evidence is conclusive: Vioxx can kill. But proving this on a case-by-case basis is difficult.

With those victories under their belt, Merck's lawyers felt confident enough to settle the remaining cases. They offered \$4.85bn in compensation; in November 2007, lawyers representing most of plaintiffs accepted. The sum will be spread between about 50,000 claimants, their lawyers, who will receive a third, and the health insurers who paid for the drug.

A SEPARATE AFFAIR

Three days before his 65th birthday and four months before Vioxx was withdrawn, Eric Barnes woke with chest pains. He was a fit British man who played and coached badminton several times a week and worked in a shop close to his home in Newton Abbot, Devon. He had been taking Vioxx to ease the arthritis in his knees. He had no history of heart problems and thought the pain was due to an upset stomach. Later that day, doctors told him he had suffered a heart attack. A short walk, perhaps a couple of hundred metres, is now the most he can manage between rests.

A few months earlier, Lynn Massey-Davis received a late night call. Her mother Marlene had been admitted to hospital in Wolverhampton. By the time Massey-Davis could get there, her mother was dead. Marlene had been taking Vioxx to combat a rare form of arthritis. She did not drink or smoke and had normal cholesterol levels—yet she died of a heart attack.

If they were US citizens, Barnes and Massey-Davis would probably be eligible for a share of the settlement. But US courts will not hear Vioxx compensation claims from anyone outside the US. Around 400 people in Britain are waiting to hear whether they will get legal aid to fund a challenge in the courts. They are predominately elderly and, if they do not get government support, may not be able to bring a case at all. So despite providing almost \$5bn to settle in the US, it is possible that Merck will not have to pay a penny to victims in Britain.

Which brings us on to another remarkable thing about Vioxx: it appears not to have done much financial harm to Merck or its bosses. During the five years it was on the market, Vioxx earned Merck around \$10bn in sales in the US alone. Merck will not reveal the costs associated with Vioxx, but industry data suggests it costs around \$1bn to develop a new drug. Merck also spent hundreds of millions of dollars a year advertising Vioxx. Other costs, such as manufacturing and distribution are harder to gauge. But added up, it becomes clear that

despite making what is probably the most expensive settlement in the history of the pharmaceutical industry, Merck did not lose much, if anything, on Vioxx. And it wasn't only Merck's balance sheet that emerged unscathed—so did the senior staff. Scolnick left the board in December 2002 to take up a research position within the company. He had earned \$6.6m in pay and bonuses since the launch of Vioxx. He now serves on the board of several investment and pharmaceutical companies. Gilmartin continues in other roles too. He is a director on the board at Microsoft. In July 2006 he was given a professorship at Harvard Business School. In his last seven years at Merck, his pay and bonuses exceeded \$20m. Merck has refused to say if anyone was internally disciplined over the Vioxx affair. To date, no one has been prosecuted.

LESSONS LEARNED?

What do the Vioxx documents tell us? The obvious answer is that the regulation of drugs is a mess. Merck handed over much of the data required by the FDA and its British equivalent, yet still the dangers were not spotted until too late. There is a simple way to fix this. Every aspect of every drugs study involving humans should be made public. It would have been far harder for Merck to have been selective about the results of the Vioxx trials if the raw data had been placed in a public database. When Merck's marketing department made claims about Vioxx's safety, anyone with an interest in the answer would have been able to check the real data, and the dangers of the drug would have become clearer years earlier.

The documents also tell us something about scientists and human nature. It is no surprise that marketing divisions spin results, but we expect scientists to be objective. This assumption is dangerous. The company's researchers did not receive an edict from the board demanding a cover up, or an email suggesting the deaths of patients be ignored. In fact, several senior Merck staff say their own relatives were taking Vioxx up until its withdrawal. The problem was that so many scientists at Merck stood to gain if Vioxx did well. When it came to judging risks, risks that in many cases were borderline and could be ascribed to other causes, they were unable to make the right call.

Similar muddles continue in drug companies around the world today. Managers are exchanging emails like the one Scolnick sent on 9th March 2000, the day he received the Vigor data, in which he told three colleagues that the cardiovascular problems were "clearly there." He was concerned, and discussed further experiments that might reveal more about the risk. Then, just before signing off, he made a prediction about Vioxx and other drugs in its class that Merck hoped to commercialise. "The class will do well," wrote Scolnick, "and so will we." ■

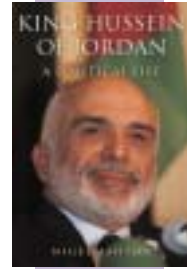
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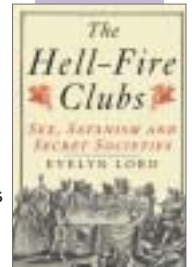
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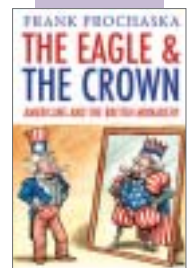
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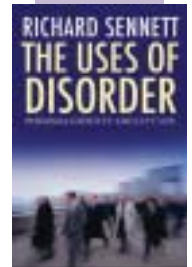
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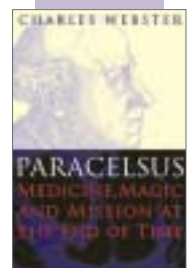
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