The safety catch

The past year has seen a beleaguered Food and Drug Administration publicly denounced as unable to protect the US public. As the political pressure mounts, Meredith Wadman joins the the agency's hunt for a remedy to its ills.

A telling scene unfolded in the lobby of a suburban Maryland hotel on 18 February. On the third and final day of a gruelling public conference, expert advisers to the US Food and Drug Administration (FDA) held in their hands the fates of three blockbuster painkillers, known as COX-2 inhibitors. To make their assessment, the experts had to balance the drugs' value in treating arthritis against mounting evidence that they cause heart attacks and strokes. Billions of dollars in revenues for drug companies — and the welfare of millions of patients — hung in the balance.

But when a mid-morning break was called and the 32 advisers wandered out for coffee, they were largely ignored by the throng of reporters at the event. Instead, the journalists clustered around a boyish-looking FDA scientist who was holding forth for a television camera. They plied him with questions about his views on the issues before the panel, diligently jotting down his every response.

In the middle of the media scrum was David Graham, a career physician at the FDA. Graham came to public prominence last November at a US Senate hearing, when he pronounced his employer "incapable" of ensuring the safety of drugs after they were approved for sale in the United States.

His scathing testimony set alarm bells ringing on Capitol Hill and raised some fundamental questions about the FDA: is the agency scientifically, structurally or politically capable of ensuring the safety of some 10,000 pharmaceuticals now used by Americans? Or has the complexity, size and pace of the business, and the power of the drug manufacturers, exceeded the regulator's ability to cope?

Graham had told senators on 18 November that just one of the COX-2 inhibitors — Vioxx — had caused at least 26,000 deaths from heart attacks in the five years before Merck withdrew it from the market last September. An epidemiologist in the FDA's Office of Drug Safety, Graham had conducted a study using the massive database of Kaiser Permanente, a health-maintenance organization based in California. Last August, armed with its results, he warned his bosses that high doses of Vioxx significantly increased the risk of heart attack and sudden death. The agency did not act — and even approved the drug's use in children with rheumatoid arthritis in the weeks before Merck withdrew it.

The FDA's Office of New Drugs — where any new medicine must pass muster before it can be sold — approved Vioxx in 1999. It was heavily promoted by Merck as an alternative to standard arthritis medications because it didn't cause stomach bleeding, and it soon became a huge success, with worldwide sales of $2.5 billion in 2003 alone. Then, last September, a Merck-sponsored trial examining whether the pill might prevent precancerous colon tumours found that Vioxx doubled the risk of heart attacks and strokes in patients using it for more than 18 months.

Critics — including plaintiffs in the raft of lawsuits against Merck that swiftly followed the drug's withdrawal — complained that as early as 1999, studies had flagged Vioxx's potential for causing heart attacks and strokes. They implied that the FDA should

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have identified the problem and pulled the medicine from the market.

In his Senate testimony, Graham endorsed that point of view. He added that Vioxx was probably far from a one-off event. It was bound to repeat itself, he said, because the FDA's organizational structure and corporate culture were biased towards approval of new drugs. Safety monitoring of drugs already out there, he said, took second place.

Graham further complained that the reviewers at the Office of New Drugs who approve therapeutics in the first place have a vested interest in the drugs' success, and are liable to ignore or overrule post-market safety concerns raised by staff scientists in the smaller Office of Drug Safety. Asked to identify other established drugs about which he had serious safety reservations, Graham named five, including Pfizer's Bextra, another COX-2 inhibitor. "The FDA as currently configured," he concluded, "is incapable of protecting America against another Vioxx. We are virtually defenceless."

Rapid response

The initial congressional response was swift and emphatic. Senator Chuck Grassley (Republican, Iowa), chairman of the Senate Committee on Finance where Graham testified, chided the FDA for ignoring danger signals and failing to heed the warnings of its own scientists. Senator Michael Enzi (Republican, Wyoming), who chairs another Senate committee with direct jurisdiction over the FDA, scolded its officials at a hearing earlier this month saying that "doing nothing to address the current controversies is not an option". Grassley is shortly expected to introduce legislation, together with Senator Christopher Dodd (Democrat, Connecticut), that would boost the power and autonomy of the Office of Drug Safety.

Yet top FDA officials say that the agency's performance remains strong. "The safety of the drug supply right now is better than it has ever been," says Janet Woodcock, the FDA's acting deputy commissioner for operations, who from 1994 to 2004 ran the agency's Center for Drug Evaluation and Research (CDER), which houses both the Office of New Drugs and the Office of Drug Safety.

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Woodcock argues that some agency critics fail to understand that risk and benefit are inextricably linked for any drug — and that calls to assess one without the other betray this basic misunderstanding. The point, she says, isn't that some drugs with risky side effects shouldn't be approved, but that their risks and benefits need to be carefully weighed both by the regulatory authorities who first approve them and by the physicians and patients who ultimately use them.

And despite the wave of bad publicity that shrouded the FDA last winter, its public image remains fairly healthy. For decades, polls have suggested that its public approval hovers at the heady level — for a government agency — of about 75%. And a February survey of 1,200 people by the Kaiser Family Foundation found that 77% thought the agency was doing a reasonable job of ensuring drug safety.

Nonetheless, by almost any measure, the past year has been a rocky one for the FDA. In March 2004, Mark McClellan decamped after just 17 months from a commissioner's position that had sat vacant for nearly two years prior to his arrival. Soon after that, the agency came under fire for suppressing the report of a staff scientist who cautioned that popular 'SSRI' antidepressants could cause suicidal tendencies in young people. And in early October, just a few days after Merck withdrew Vioxx, the FDA's competence in ensuring the safety of vaccines destined for the US market was called into question when British authorities abruptly closed a flu vaccine plant in Liverpool owned by US company Chiron. This halved the United States' supply of vaccine for the coming winter and provoked a public uproar.

David Kessler, who ran the agency from 1990 to 1997 and is now dean of the medical school at the University of California, San Francisco, thinks that the cumulative impact of events has been considerable. "It certainly began to shake confidence, not only in the public but within the medical community," Kessler says. "For the first time, I have physician colleagues asking me if they can believe what the FDA is saying."

Full stretch

Some of the 1,600 scientists and physicians who work at the CDER privately admit that they are stretched to fulfil the agency's mission. With an average annual salary of $128,000, many are forsaking more lucrative careers in the private sector — often because they find FDA work satisfying and valuable.

"I tell my kids I have one of the most interesting jobs in the world," says Rachel Behrman, a physician who began working as a drug reviewer in 1989 and is now deputy director of the CDER's Office of Medical Policy. "And I go to bed every night thinking I've done something important."

But the current crises, combined with the fact that 30% of the FDA's work force is eligible for retirement over the next five years, has agency-watchers worried that retention of high-quality staff is going to become a tough challenge. "If we continue to pound and beat up on the agency, we are going to lose very good people," says Kessler.

Worries about the pressure on FDA staff surfaced in 2002, when the Government Accountability Office assessed the impact of a 1992 law that introduced industry fees to pay for speedier drug reviews. It found that

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FDA

Balancing act: Janet Woodcock argues that the key to drug regulation is weighing up risks and benefits.

the law had boosted reviewer workloads, cut their training and resulted in annual attrition rates among FDA scientists of about 10% — roughly twice the level found at the National Institutes of Health or the Centers for Disease Control and Prevention.

And a survey of 400 FDA scientists conducted for another 2002 government study — but not published until December 2004, when it was accessed by the Union of Concerned Scientists under the Freedom of Information Act — found a group of people seriously concerned about the agency's ability to protect the public from dangerous side effects in approved drugs. In that survey, 19% said that they were "not confident at all" in the FDA's ability to monitor the safety of drugs once they are on the market; only 6% were "completely confident" in that ability. And 18% said that they had been pressured to approve new drugs despite reservations about their safety, efficacy or quality.

Testing times

The COX-2 controversy has left some observers asking whether the CDER, with an annual budget of about $500 million, has the resources to police a prescription drugs market that is now worth more than $160 billion annually in the United States. Some also argue that the FDA lacks the legal authority it needs to monitor established drugs.

Before a drug is approved, the onus rests on the manufacturer to demonstrate its safety and efficacy. Once the FDA approves a medicine for marketing, that balance shifts. The agency can ask — but not require — companies to pay for and conduct post-market safety studies; and it cannot limit the use of a drug to particular medical subspecialities, as it can with medical devices. Nor does it have explicit authority to beef up warnings on drug labels. Instead, it negotiates label changes in often-protracted discussions with manufacturers. In the case of Vioxx, a change to the label to include a "precaution" about the risk of heart attack at high doses took 18 months for the agency to negotiate with Merck.

That kind of outcome begs for additional legal muscle for the FDA, says William Schultz, a Washington lawyer who was the agency's deputy commissioner for policy in the mid-1990s. "It's the post-market piece that really needs the attention," he says. "Patients have got to realize how little we know when a drug goes on the market."

There are other thorny problems in ensuring post-market safety. The FDA, for example, doesn't set out systematically to monitor dangerous side effects. Instead, it relies on a reactive, 'passive' reporting system in which doctors report possible cases of side effects only when it occurs to them that a particular ailment may be the reaction to a drug. The system, by its nature, will seldom detect dangerous side effects that are already common in the population, such as the heart attacks and strokes prompted by the COX-2 inhibitors (see page 557). It is thought that the 400,000-odd reports that the FDA gets in this way each year represent only a small fraction of actual adverse events.

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Then there is the fact that the 1992 law that instituted industry-paid fees did so on the condition that the FDA met tight drug-review timelines and otherwise boosted performance standards. To achieve this — and so keep hundreds of millions of dollars in industry fees flowing into the agency — the drug centre was forced to raid other budgets. The upshot: in President Bush's proposed 2006 budget, new-drug review consumes roughly 80% of the CDER's budget; only about 6% of it is designated for post-market surveillance.

The 1992 law "sapped resources from other very needed areas, away from drug safety, away from compliance", says Kessler. Post-market monitoring "absolutely needs more resources. You can't just have resources go into new drug review", he adds.

Independent thought

In at least some quarters on Capitol Hill, that message is being heard. The bill being drawn up by Grassley and Dodd would create a fully funded Center for Drug Safety independent of the CDER with authority to demand label changes from drugmakers. "It doesn't make sense to have the office that reviews the safety of drugs under the thumb of the office that puts the drugs on the market in the first place," Grassley told the Consumer Federation of America last month.

Acting FDA commissioner Lester Crawford, who has been nominated by President Bush for the permanent post, told senators at his nomination hearing on 17 March that he is "open to discussing" an independent office of drug safety. Crawford has also announced that a new board for overseeing drug safety — an advisory board of mainly FDA employees — will publicize worrisome side effects more quickly than has happened in the past. Critics immediately assailed the board as toothless, because it will lack the power to require label changes or to pull drugs from the market. But Crawford says that it will herald a new era of public openness at the agency.

Still, some agency-watchers fear that the relatively low profile of Crawford's nomination and confirmation process, together with the reluctance of the conservative Congress to antagonize its allies in industry, suggest that even the tens of thousands of deaths attributed to Vioxx may be insufficient to initiate any real strengthening of the FDA.

The agency's history demonstrates that "major changes come after disasters", says Schultz. And the Vioxx case may not rise to that threshold in the public mind. At the end of the three-day advisory panel meeting back in February, the experts voted narrowly to allow Vioxx back onto the market, subject to careful constraints. They also voted to give patients continued access to Pfizer's two COX-2 inhibitors, Celebrex and Bextra.

Graham, for one, was not impressed. "Despite the biggest drug-safety catastrophe in the history of the United States," he noted with his trademark earnestness, "people are heavily invested in the status quo." ■

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