

## Vioxx, the implosion of Merck, and aftershocks at the FDA



Today we publish results from a cumulative meta-analysis which show that the unacceptable cardiovascular risks of Vioxx (rofecoxib) were evident as early as 2000—a full 4 years before the drug was finally withdrawn from the market by its manufacturer, Merck. This discovery points to astonishing failures in Merck's internal systems of post-marketing surveillance, as well as to lethal weaknesses in the US Food and Drug Administration's regulatory oversight. In a recent Editorial, we commended Merck for acting promptly in the face of new findings about the safety of Vioxx.<sup>1</sup> Our praise was premature. The evidence showing that Vioxx caused significant adverse events was apparent well before data from the APPROVe trial triggered Merck's overdue intervention. This week's report by Peter Jüni and colleagues will add significant weight to ongoing litigation against Merck by patients who believe they were harmed by this drug.

These findings also come in the wake of new disclosures that suggest Merck was indeed fully aware of Vioxx's potential risks by 2000. Investigations by the *Wall Street Journal*<sup>2</sup> have revealed e-mails that confirm Merck executives' knowledge of their drug's adverse cardiovascular profile—the risk was “clearly there”, according to one senior researcher. Merck's marketing literature included a document intended for its sales representatives which discussed how to respond to questions about Vioxx—it was labelled “Dodge Ball Vioxx”. Given this disturbing contradiction—Merck's own understanding of Vioxx's true risk profile and its attempt to gloss over these risks in their public statements at the time—it is hard to see how Merck's chief executive officer, Raymond Gilmartin, can retain the confidence of the public, his company's most important constituency.

The FDA's position is no less comfortable. The public expects national drug regulators to complete research, such as that published by Jüni and colleagues, in their ongoing efforts to protect patients from undue harm. But, too often, the FDA saw and continues to see the pharmaceutical industry as its customer—a vital source of funding for its activities—and not as a sector of society in need of strong regulation.

Worse still, the FDA's Office of Drug Safety co-exists in the same centre—the Centre for Drug Evaluation and Research (CDER)—as the Office of New Drugs, the part of the agency that works most closely with industry to license new medicines. Once a licensing approval has been made it is naturally in CDER's own interests to stand by its original decision. CDER's reputation would be damaged if its licensing judgments were constantly challenged by its own staff. This understandable but dangerous tendency to discourage dissent makes the Office of Drug Safety, which sits lower in the hierarchy of CDER than the Office of New Drugs, weak and ineffective. The inherent precedence that licensing of

new drugs takes over safety evaluation is a serious flaw in FDA's complex regulatory structure.

In the case of Vioxx, FDA was urged to mandate further clinical safety testing after a 2001 analysis suggested a “clear-cut excess number of myocardial infarctions”.<sup>3</sup> It did not do so. This refusal to engage with an issue of grave clinical concern illustrates the agency's in-built paralysis, a predicament that has to be addressed through fundamental organisational reform.

On Nov 2, 2004, the FDA tried to shore up its tarnished reputation by posting on its website an early version of a recently completed observational study into the safety of Vioxx. The report comes with a warning that it has “not been fully evaluated by the FDA and may not reflect the official views of the agency”. The FDA investigators estimate that over 27 000 excess cases of acute myocardial infarction and sudden cardiac death occurred in the USA between 1999 and 2003. “These cases”, they write, “would have been avoided had celecoxib been used instead of rofecoxib”. This study is presently under review at *The Lancet*. It is unclear why the FDA could not have waited for the fully evaluated report to have been scrutinised, revised, and published according to the norms of scientific peer review. Bypassing independent peer review smacks of panic in the FDA, which is under intense reputational pressure. And yet its decision to try to undermine the integrity of this work again shows that the agency's senior management is more concerned with external appearance than rigorous science.

The licensing of Vioxx and its continued use in the face of unambiguous evidence of harm have been public-health catastrophes. This controversy will not end with the drug's withdrawal. Merck's likely litigation bill is put at between US\$10 and \$15 billion. The company has seen its revenues and market capitalisation slashed. It has been financially disabled and its reputation lies in ruins. It is not at all clear that Merck will survive this growing scandal.

But the most important legacy of this episode is the continued erosion of trust that public-health institutions will suffer. Failure to act decisively on signals of risk might minimise short-term political criticism for regulators, or shareholder unrest for company chief executives. But the long-term consequence of prevarication is a tide of public scepticism about just whose interests drug makers and regulators truly represent.

It is no good saying, as some academic physicians have said to me, that one must expect pharmaceutical companies to do all they can to protect their products, even in the face of clear evidence of risk. And it is of little help to suggest that regulators have a nearly impossible job of balancing harms and benefits. Defenders of our systems of drug regulation argue that the blame for the Vioxx debacle in-

Published online  
November 5, 2004  
<http://image.thelancet.com/extras/04cmt396web.pdf>  
See [Articles](#)

stead rests on allegedly credulous specialists who should have asked tougher questions about the drug they were prescribing. Why clinical investigators studying Vioxx did not do more to raise concerns is a fair question that needs to be answered. But in doing so, we must not diminish the importance of the covenant of trust that society has established with powerful commercial and governmental institutions. For with Vioxx, Merck and the FDA acted out of ruthless, short-sighted, and irresponsible self-interest.

*Richard Horton*

*The Lancet*, London NW1 7BY, UK

- 1 Editorial. Vioxx: an unequal partnership between safety and efficacy. *Lancet* 2004; **364**: 1287–88.
- 2 Matthew AW, Martinez B. E-mails suggest Merck knew Vioxx's dangers at early stage. *Wall Street Journal* Nov 1, 2004: A1.
- 3 Topol EJ. Failing the public health—rofecoxib, Merck, and the FDA. *N Engl J Med* 2004; **351**: 1707–09.