# Vioxx: an unequal partnership between safety and efficacy

Rofecoxib (Vioxx) is, or was, Merck and Co's leading drug for control of acute pain, and pain associated with osteoarthritis, rheumatoid arthritis, and menstruation. Last year worldwide sales of rofecoxib reached US$2·5 billion following the most impressive global sales growth for any drug in 2001. Last week, after urgent discussions with the US Food and Drug Administration (FDA), Merck felt compelled to withdraw rofecoxib after its most recent trial, APPROVe (Adenomatous Polyp Prevention On Vioxx), showed an adverse cardiovascular side-effect profile. For Merck to act so promptly in the face of these most recent safety concerns is commendable and should serve as an example of responsible pharmaceutical industry practice. However, the short history of cyclooxygenase (COX)-2 inhibitors has been plagued by persistent safety concerns. The question that must now be answered is why has it taken so long for Merck and government drug regulators to address these signals properly?

The story of COX-2 inhibitors began for clinicians and their patients in 1999 with the licensing of two first generation drugs, rofecoxib and celecoxib, by the FDA. Their primary indications were for the control of pain associated with several different conditions and their debut was announced in 2000 in the medical literature with two landmark trials: VIGOR for rofecoxib, and CLASS for celecoxib. Subsequently, a number of second generation COX-2 inhibitors have been developed. These include valdecoxib, parecoxib, etoricoxib, and lumiracoxib. The indications for their use have remained largely unchanged and more "me-too" COX-2 inhibitors are on the horizon.

From the outset, questions have been raised about the safety profile of these drugs. Although the CLASS trial did not find a difference in the incidence of cardiovascular side-effects between celecoxib and ibuprofen or diclofenac, the VIGOR trial revealed a significant increase in the number of myocardial infarctions in patients taking rofecoxib compared with those receiving naproxen. These concerns were crystallised the following year by Debabrata Mukherjee, Steven Nissen, and Eric Topol in *JAMA* in their review paper specifically highlighting the cardiovascular side-effect profile of COX-2 inhibitors. Concerns were shared by the FDA, who implemented labelling changes in 2002 to reflect the findings from the VIGOR trial. However, even following these warnings, and in the face of mounting evidence for the cardiovascular side-effects of rofecoxib, aggressive direct-to-consumer marketing of this questionable drug continued unabated.

What then finally tipped the balance in the risk-benefit equation leading to last week's dramatic global withdrawal of rofecoxib? APPROVe was a multi-centre, randomised, placebo-controlled, double-blind study investigating the effects of rofecoxib on the recurrence of neoplastic large bowel polyps in 2600 patients with a previous history of colorectal adenoma. It was stopped prematurely on the instruction of the data and safety monitoring board after the investigators found that after 18 months treatment, patients taking rofecoxib had twice the risk of a myocardial infarction compared with those receiving placebo. Advice is now being issued to pharmacists and doctors in each of the 80 countries where rofecoxib is marketed to stop prescribing the drug with immediate effect. 2 million patients already taking rofecoxib will be contacting their physicians to discuss discontinuing treatment—a busy and anxious time for doctors around the world.

A key question remains as to why it took this risk to be identified from a relatively small trial investigating a novel use for rofecoxib, after it had been licensed for several years and prescribed to so many patients? Although Peter Kim, president of Merck Research Laboratories, recently said "Merck has always believed that prospective, randomized, controlled clinical trials are the best way to evaluate the safety of medicines. APPROVe is precisely this type of study . . . ", it is unlikely that APPROVe was designed and executed with a general safety assessment as its primary goal. A further question relates to the safety of the other COX-2 inhibitors being actively marketed today. Although the TARGET trial published in *The Lancet* in August this year, and the largest COX-2 trial to date, failed to demonstrate a statistically significant difference in cardiovascular side-effects between lumiracoxib and naproxen or ibuprofen, more people taking lumiracoxib had a myocardial infarction.



See *N Engl J Med* 2000; **343:** 1520–28; and *JAMA* 2000; **284:** 1247–55

See **Articles** *Lancet* 2004; **364:** 665–674, 675–84; and **Comment** *Lancet* 2004; **364:** 639–40

See *JAMA* 2001; **286:** 954–59

Doctors need to be more aware of the very preliminary nature of data, both for safety and efficacy, provided with newly licensed drugs. For rofecoxib the original safety data were based on results from approximately 5000 patients. In comparison with the 2 million people receiving the drug until last week, this is a very small number and helps to explain how an important side-effect could have been missed, and subsequent confidence in the drug misplaced. For all newly licensed drugs, confidence about safety can only be provisional.

Pharmaceutical companies also have lessons to learn. Merck responded well to this latest piece of the rofecoxib jigsaw puzzle. However, the real picture of cardiovascular risk has been apparent for some time and Merck's vigorous defence of this drug in the past was clearly an error. If the dangers associated with rofecoxib were not proven, they were certainly possible, even probable, given the available data, and it should not have been left to a small trial in a novel application to reveal them. In the end it is patients, now understandably confused by the implications of rofecoxib's withdrawal, who will lose the most. Which drugs, they will ask, should they trust?

Finally, drug regulators must now reassess the safety and efficacy thresholds required for the licensing of a new pharmaceutical product. Clearly, this is an immensely complicated equation involving, among other factors, the nature of the condition being treated, the therapeutic strategies already available, and the perceived benefit-to-hazard ratio of the new treatment. The Vioxx story is one of blindly aggressive marketing by Merck mixed with repeated episodes of complacency by drug regulators. We need clear statements from all parties in this sorry tale about the lessons to be learned. Without more vigilant drug regulation in the future, doctors will continue to be misled and patients' lives will continue to be endangered. ■ *The Lancet*

# A steppe towards a cooler world

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Still Pictures

On Sept 30, Russia's President Vladimir Putin gave the kiss of life to the embattled 1997 Kyoto Protocol on greenhouse-gas emissions by having his cabinet approve ratification of the treaty. The Russian parliament will in all likelihood concede Putin's wishes. With the USA, the world's largest greenhouse-gas emitter (over a third of the 1990 total) withdrawing from the treaty in 2001, Putin's resuscitation is extremely important.

With Russia signing up to the Protocol—ratification is expected early next year—enough signatories will exist for the treaty to come into force. With that comes the binding agreement for 36 industrialised countries to reduce their collective emissions of six greenhouse gases (mostly carbon dioxide, and from motor vehicles, power stations, and factories) by at least 5% of their 1990 levels, by 2008–12. The targets are achievable and beyond: the UK's target of a 12·5% reduction has already been surpassed (it is now 14·5%). Without reductions in greenhouse gases, the world will see more and more respiratory and cardiovascular diseases, cancer, and, as a result of climate change, global shifts and increases in infectious diseases previously confined to the tropics.

One US Governor has outed himself as an opponent to Bush on climate matters. The Republican Arnold Schwarzenegger, a Bush fan in most respects, seems an unlikely bedfellow for Putin, but he has pitched California in with other US states in a legal battle to make Bush say that carbon dioxide is a pollutant, which would force the Government to act. Schwarzenegger is also playing one of the good guys, in a state where the car rules. He is backing plans to reduce carbon dioxide emissions from cars in California.

Russia's signing of the protocol, itself criticised for being insufficient and not tackling pollution from the developing world, is only a start. And Putin is not being completely altruistic—his new green credentials are designed to impress the European Union enough for them to support Russia's entry to the World Trade Organisation. But other Kyoto signatories will now start falling into line. Japan, the world's fourth worst polluter, with a new tax this year on the use of fossil fuels, will now be on notice to do more. Putin sends a strong message to that other renegade country: the USA, and a new president perhaps, must face up to its responsibilities as the world's worst polluter. ■ *The Lancet*