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cardiovascular risks of Vioxx (rofecoxib) were evident as early as 2000—a full 4 years before the drug was finally withdrawn from the market by its manufacturer, Merck.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.1 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 Juni 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 Journal2 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 Juni 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”. 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-
Buying health in Honduras

Governments have a long history of announcing lofty and well-meaning pledges to make the world a healthier place. The 1970s had its noble but ineffectual Health for All declaration at Alma-Ata. After falling miserably short of the visionary goal of Alma-Ata and many goals that followed, the international community ushered in the new millennium with its Millennium Development Goals (panel). These goals are supposed to be achieved by 2015. Unfortunately, unless something dramatically changes, there seems little doubt that they will not be reached. One dramatic change worth considering is reported by Saul Morris and colleagues in today’s Lancet. They compared poor Honduran mothers and children who were paid money if they obtained preventive health services with those who did not receive payments. Those receiving conditional payments used child-survival interventions to a greater extent than those in the control population.

The use of monetary incentives to entice people to adopt healthy behaviour or to use preventive health services is a dramatic break from the usual way we try to improve a population’s health. The dominant model for improving public health focuses almost exclusively on the supply side of the health equation by improving the quality of services, expanding coverage, and telling people why they should use the health services and where they can get them. The underlying assumption of this traditional approach is that people want to remain or become healthy and they will use good health services if they know about them. This strategy has had indifferent results in much of the developing world. Its muddling performance has been especially frustrating in areas such as child survival, where progress in driving down mortality rates has stalled, even though we have effective mortality-reducing interventions.

Equally exasperating is our persistent inability to close the health-inequity gap between the poor and well-to-do.

The Honduran programme, which is funded through an Inter-American Development Bank loan, is similar to programmes found in five other Latin American countries. The programme addresses the failure of the health system by paying people to take their children to preventive health services and to attend schools. Economists call these payments conditional cash transfers. They seem to work. In Nicaragua, 90% of children less than 3 years of age living in the intervention area for conditional cash transfers participated in a nutrition-monitoring programme while only 67% did so in the control area. In Columbia, the proportion of children under 6 years of age participating in a growth-monitoring programme increased by 37%.

An important and refreshing characteristic of conditional-cash-transfer projects is their rigorous evaluation component, which frequently uses randomised trials. This emphasis on documenting cost-effectiveness has been spurred on by the World Bank, the International Food Policy Research Institute, and the Inter-American Development Bank, which promote conditional cash transfers as a way to reduce intergenerational poverty and improve health in poor communities. Healthy and educated children are more likely to be productive and to break out of the cycle of poverty suffered by previous generations.

Most of the research on conditional cash transfers has not yet appeared in peer-reviewed journals, a fact that might have contributed to the approach not being widely appreciated outside of Latin America. However, considering the extensive grey literature found on the websites of supporters and funders of conditional cash transfers, I have little doubt that monetary incentives are a cost-effective way to increase the use of preventive health services in poor countries. This assessment is shared by many policy-makers in Latin America. For example, Mexico’s Progresa programme

Panel: Health Millennium Development Goals

- Reduce by two-thirds, between 1990 and 2015, the under-5 mortality rate
- Reduce by three-quarters, between 1990 and 2015, the maternal mortality ratio
- Halt by 2015 and begin to reverse the spread of HIV/AIDS
- Halt by 2015 and begin to reverse the incidence of malaria and other major diseases

Richard Horton
The Lancet, London NW1 7BY, UK