EMBO reports

analysis

First do no harm

Improving drug safety through legislation and independent research

The Hippocratic Oath extols physicians "to first do no harm." So, doctors weigh the risks of using a drug—including its side effects—against its benefits for an individual patient. However, as medicines have become more powerful, the risk of side effects has increased: the number of serious and fatal drug-related events reported to the US Food and Drug Administration (FDA; Bethesda, MD, USA) increased 2.6-fold and 2.7-fold respectively, between 1998 and 2005. Furthermore, the number of serious events increased four times faster than the volume of prescriptions (Moore *et al*, 2007). These developments—together with a recent spate of highly publicized drug withdrawals—raises several fundamental questions. How can patients be sure that the drugs they take are as safe as is practicable? Do regulating authorities and companies act as quickly as possible to address safety problems that emerge after a drug has been approved? What could be done to improve the regulatory system to better protect patients?

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The withdrawal of Vioxx® (rofecoxib; Merck, Whitehouse Station, NJ, USA)—a selective cyclo-oxygenase (COX) 2 inhibitor—provided a wake-up call for regulatory authorities (Greener, 2005). After the FDA approved Vioxx in 1999, around 80 million people worldwide used the drug to treat arthritis and other conditions characterized by chronic pain. In September 2004, Merck withdrew the drug following evidence that long-term use of Vioxx increased the risk of heart attack and stroke. David Graham, Associate Director for Science and Medicine at the FDA's Office of Drug Safety, estimates that Vioxx caused between 88,000 and 138,000 additional heart attacks or sudden cardiac deaths in the USA, and that 30–40% of patients who suffered cardiovascular problems because of Vioxx probably died. As Graham famously told the US Senate in 2004: "If there were an average of 150 to 200 people on an aircraft, this range of 88,000 to 138,000 would be the rough equivalent of 500 to 900 aircraft dropping from the sky" (US Senate, 2004).

Despite these large numbers, the absolute increase in risk was small. VIGOR, one of the first studies to link rofecoxib with cardiac problems, found that 0.4% of the patients who were taking Vioxx suffered a heart attack, compared with 0.1% of those taking naproxen—a standard anti-inflammatory drug (Bombardier *et al*, 2000). Yet, because tens of millions of people in more than 80 countries took Vioxx, this small risk translated into an important public health issue.

Such problems are, in part, unavoidable. "Common, severe, early side-effects are easily assessed and recognized in clinical trials," said Angel Mazon from the Children's Hospital at the Universitari La Fe in Valencia, Spain. "However, the less common, long-term, more subtle effects are more difficult and expensive to study. Studying these adverse events is out of the reach of most independent investigators and we have less confidence in our understanding of these risks when the drug is launched."

Clearly, it is impractical to simply increase the size of most phase III trials—the large pre-launch investigations—to detect uncommon adverse events. "We keep repeating the old mantra of pre-marketing studies being too small and too short to detect rare adverse events," commented Yoon Loke, Senior Lecturer in Clinical Pharmacology at the University of East Anglia in Norwich, UK. "But increasing the size isn't necessarily the answer. We need some new thinking."

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Thus, physicians rely, partly, on follow-up 'pharmacovigilance' trials or 'post-marketing surveillance' (PMS) studies and, partly, on spontaneous reports of adverse events in order to ensure that the drugs are safe. However, PMS studies are usually sponsored and designed—at least in part—by the manufacturer, which raises concerns about independence and bias in the study design. In addition, regulatory agencies and companies watch for adverse events once a drug reaches the market and more people are exposed to it. Therefore, one might expect such pharmacovigilance systems to be sufficiently sophisticated and responsive. Not so, according to Loke: "Pharmacovigilance systems are bloated and slow-moving, unable to keep up with the times."

Indeed, the withdrawal of Vioxx and a more recent row over Avandia® (rosiglitazone; GSK, Brentford, UK), which is used to treat type II diabetes, have further undermined the confidence of patients and physicians in the ability of current systems to ensure safety. A meta-analysis suggested that rosiglitazone increases the risk of myocardial infarction by 43% and deaths from cardiovascular causes by 64% (Nissen & Wolski, 2007)—although the latter did not quite reach statistical significance. "The Avandia affair undermined the confidence that patients have in the drugs

they take and in the physicians who prescribe those drugs. It cast further doubt on the ability [of regulatory authorities] to protect patients from harm," wrote Robert Misbin, the FDA's medical officer who initially reviewed the application for rosiglitazone (Misbin, 2007).

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After reviewing the new data, the European Medicines Agency (EMEA; London, UK) concluded that the benefits of rosiglitazone continued to outweigh its risks, but updated the prescription information accordingly (EMEA, 2007). However, it might take more than an EMEA review to restore confidence. "All stakeholders need to regain an appropriate perspective in the wake of the Avandia concerns," commented Jeffrey Stoddard, Vice President of Medical and Scientific Affairs at Covance (Princeton, NJ, USA)—a contract research organization that provides preclinical, clinical and post-marketing services for pharmaceutical companies. "If a molecule is biologically active, some risk must come along with whatever benefits it has. Knowing and understanding the risks and benefits is crucial. To restore confidence, stakeholders need to work together to define and educate patients and physicians about these issues."

Nevertheless, a large part of the problem lies in identifying new health risks in the first place. "Vioxx is often quoted as an example of the failure of regulators to detect an adverse reaction once a medicine is marketed—but trying to differentiate between the effects of a medicine and the 'normal' events that occur in everyday life is not always straightforward," the EMEA commented by e-mail. Many middle-aged people suffer heart attacks and the same age group typically took Vioxx; therefore, ascribing causality is difficult.

Traditionally, regulatory agencies relied on health care professionals to send reports of suspected adverse events to the company or a central 'clearing house'. Statisticians then analysed these reports to identify 'signals' that might herald uncommon and rare adverse events. Thus, the recent decision to withdraw another COX2 selective drug, Prexige® (lumiracoxib; Novartis, Basel, Switzerland), after reports suggested that it caused liver damage, seems to validate spontaneous reporting. Regulators and Novartis received 159 spontaneous reports of suspected adverse reactions among patients taking lumiracoxib. Of these, 91 were serious and 2 were fatal. To put this in context, doctors worldwide wrote more than 8.5 million prescriptions for lumiracoxib before regulators in Europe and other countries pulled it from the market.

Yet, critics of the current system maintain that the response of regulatory agencies to early reports of adverse effects is too slow. For example, around 9,000 patients took lumiracoxib during a pivotal study, published in 2004, which showed an absolute increase of 2% in abnormal liver function (Farkouh *et al*, 2004; Schnitzer *et al*, 2004). At the time, some experts raised concerns over the liver toxicity linked to lumiracoxib, whereas others remained unconvinced that there were grounds for concern. Similarly, the VIGOR study linked rofecoxib to an increased risk of serious cardiovascular events in 2000, four years before it was withdrawn from the market. "Some pharmacovigilance people consider that withdrawals and safety alerts are evidence for the good health of the regulatory process," Loke said. "I am not so sure."

Loke believes that these and other examples illustrate the over-reliance of society on spontaneous reporting. "Regulators and companies wait to see what reports drop into their letter-box," he commented. "It is time that the regulators start adopting new, more robust methodologies. Many techniques other than spontaneous reports are required to build a complete picture of a drug's safety."

The EU Risk Management Plan (EU-RMP), introduced in November 2005, should help, at least in part, to construct this picture. Companies applying for marketing authorization for most drugs must submit a RMP that reviews the current state of toxicological knowledge. In particular, companies discuss the limitations of the clinical trial population and the implications for safety that arise from differences between the patients studied and those likely to take the medicine. For example, differences in age, ethnic origins and concurrent conditions, such as renal or liver disease, can influence the toxicological profile.

"The EMEA now requires companies to provide epidemiological information about the population with the disease the drug is intended to treat," the EMEA commented. "This enables a baseline to be established on what might be expected in the population and could help in detecting adverse reactions that mimic common events. However, to work, it requires either pharmaco-epidemiological studies using record linkage databases that record all events, or extreme suspicion and dedication by doctors in reporting adverse reactions in spontaneous systems." The EU-RMP also requires the drug company to provide a pharmacovigilance plan describing how it will study identified and potential risks, how it will address missing information and how it intends to minimize as-yet-unknown risks.

But, as Loke commented, companies and regulators make little attempt to actively seek and verify signals from other sources, such as case reports published in the scientific literature. He examined 63 case reports of suspected adverse drug reactions published in 1997 in five leading medical journals. Five years later, only 17% had undergone further detailed evaluation and only 5% were backed up with data from controlled studies. Only 7 and 15 entries of the 48 agents included in the *British National Formulary* and the *Medicines Compendium*, respectively—standard UK references for physicians—reported the suspected reaction (Loke *et al*, 2006). "Perhaps companies fear that if they look a bit too closely, they might find something wrong and it [is] better to leave the data fuzzy for as long as possible," Loke said. "Relying on the pharmaceutical company to design safety studies is like asking turkeys to vote for Christmas."

Other researchers also question the reliability of studies sponsored by the pharmaceutical industry. One recent analysis found that clinical studies of inhaled corticosteroids—a mainstay of asthma care—are less likely to report adverse effects if they are funded by the industry (Nieto *et al*, 2007). Even when statistically significant differences emerge, industry-funded studies tend to give a 'more favourable clinical interpretation' of the results. The Nieto paper assessed safety reporting in 275 studies of inhaled corticosteroids funded totally or partly by the manufacturer and 229 trials that received no funding from the industry. They found that 65.1% of studies that had no pharmaceutical funding reported statistically significant differences for adverse effects between the active and control group compared with only 34.5% of pharmaceutical-funded studies. The authors classified the interpretation of adverse effects into three categories: 'no

comments,' 'absent or unimportant' and 'adverse effects need to be considered'. Among the studies that found a statistically significant increase in adverse effects, those funded by the pharmaceutical sector were almost four times more likely to conclude that the drug was safe than investigations funded from other sources.

The paper, therefore, called for more comprehensive conflict-of-interest disclosures. "If clinicians know the study's funding, they'll be better informed to draw their own conclusions," commented Mazon, who was one of the paper's authors. "Many journals now require clinical trials to be previously registered and require contracts between companies and investigators not to include clauses that could limit the rights of the latter to publish unfavourable results. This can prevent gross faults, but not the more subtle influence on interpretation of results by sponsored investigators."

In addition, Mazon called for independent organizations and agencies to fund more studies. "Legislative or administrative measures could be taken to make pharma companies provide funds for the investigation of their products. Alternatively, part of the taxes paid by pharma companies should be invested in studies concerning their products, administered by organizations or agencies, so that companies [have] no role in the investigation," he suggested. "The more the information agencies have, the more objective and more unprejudiced [the] regulator's decision will become."

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Loke agrees that there should be a greater involvement of independent researchers. "Pharmaceutical companies design studies to prove the safety of their product, they don't create a study aimed at demonstrating the degree of harm. There's a subtle but clear difference in the objectives," he noted. "The solution, of course, is to have independent experts designing and conducting safety evaluations." Loke proposed that regulators and pharmacovigilance researchers could set up a network of healthcare databases to identify and assess potential safety issues. "Using computerized databases, it would take no more than a couple of months work to find the records of, and analyse, worrying signals," he said.

Against this background, the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) plans to provide a database of independent centres that are able to conduct high-quality research into drug safety. "The project also intends to make an inventory of data resources such as record linkage databases and registries that can be used for research," the EMEA added.

However, Stoddard thinks that some of the concerns about the influence of the industry on the literature are exaggerated. "Sponsors propose defined safety endpoints, but regulatory authorities in the USA and worldwide carefully review these issues and make final pronouncements as to acceptability," he said. "Thus, regulatory authorities provide significant input and exert meaningful influence on conducting proper safety assessments. Many, many checks and balances help to ensure that safety studies sponsored by manufacturers are reliable and that the results can be trusted."

The EU-RMP also adheres to this principle. "Companies proposing studies as part of the EU-RMP are required to submit the protocols to the regulatory authorities," the EMEA commented. "It is hoped that subjecting protocols to regulatory review prior to the start of the study will ensure that studies are focussed on the important areas and are [of] high quality."

Elsewhere, regulatory processes and pharmacovigilance are undergoing a radical overhaul, partly in response to Vioxx and other high-profile cases. The EMEA noted that requiring companies to submit EU-RMPs forces them to involve their pharmacovigilance departments at an earlier stage in drug development: "Companies are frequently asked to propose studies to answer specific safety issues in the pharmacovigilance plan and the commitment to perform these studies is part of the marketing authorisation."

In the USA, the FDA Amendments Act of 2007 became law in September. This makes it more likely that drug companies will shift resources towards drug safety, pharmacovigilance, risk management, epidemiology, medical affairs and post-marketing safety surveillance and research. "The Act constitutes the most comprehensive reform of prescription drug regulation in four decades," Stoddard said. "There are few areas of drug and device development and commercialization that are not touched by this reauthorization, and the act gives the FDA considerable new authority."

Indeed, the act reflects a worldwide trend to increase the scrutiny of new medicines. "As the FDA and the EMEA co-operate more closely and harmonize their processes, they will be likely to increase their reliance on objective outside experts," Stoddard commented. "Companies will need to be able to position themselves to deal with the reality of increased authority being placed on the shoulders of these experts."

These changes should help to restore the confidence of patients and physicians in their medicines, and help authorities and companies detect and rapidly react to signals that might herald the next Vioxx or Prexige. Unfortunately, the very nature of drug development means that it is not a question of if the next case will come, but when.

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Mark Greener

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