Drug safety on trial

Last year's withdrawal of the anti-arthritis drug Vioxx triggered a debate about how to better monitor drug safety even after approval

In September last year, Merck (Whitehouse Station, NJ, USA) withdrew its anti-arthritis blockbuster drug Vioxx® (rofecoxib) after studies showed that it increases the risk of myocardial infarctions and strokes. Vioxx is, however, only the latest in a long series of high-profile drug withdrawals. Over the past few years, pharmaceutical companies voluntarily withdrew the lipid-lowering drug Lipobay® (Baycol®; cerivastatin), the anti-obesity drugs fenfluramine and dexfenfluramine, and several other medicines due to safety concerns. And that may not be the end; according to an official with the US Food and Drug Administration (FDA), there are even more drugs on the market that should be withdrawn for safety reasons. The Vioxx case has already led to a storm of criticism from members of the US Congress, medical journals and even from within the FDA, and fuelled fierce debate about how to reorganize the agency's monitoring of approved drugs so as to prevent similar cases (Harris, 2004; Frantz, 2005).

As the dust from the withdrawal of Vioxx began to settle, one thing became clear. The views of society regarding the balance between the risks and benefits of medicines has shifted, something that pharmaceutical companies, regulators and scientists need to face. This underlies the increasing emphasis on drug safety, and addressing these growing concerns probably requires changes on several fronts. Drug safety agencies may need legally enforceable phase IV studies—performed once a drug reaches the market—to follow a drug's safety and efficacy after approval. Some commentators believe that new drugs should also be granted a probationary licence that is

confirmed only if post-marketing studies show an acceptable risk–benefit profile. In addition, clinicians and doctors in private practice should become more proactive in reporting adverse events while pharmaco-epidemiologists need to collate data on drug performance from diverse sources.

At the heart of the current scrutiny of drug safety lies a fundamental shift in the way society views medicines. The Hippocratic Oath, the bedrock of medical practice, behoves doctors to 'first do no harm'. In practice, of course, patients and clinicians willingly trade adverse events for efficacy. This risk–benefit ratio depends on the drug and the condition—patients and doctors tolerate side effects for a cancer chemotherapeutic that would be unacceptable in an oral contraceptive. Nevertheless, as doctors can now choose from a diverse armamentarium of drugs, physicians' and patients' scrutiny increasingly falls on the adverse-event profile. "Thirty years ago, we wanted effective medicines. Clinicians didn't have very effective medications to reduce cholesterol levels or tackle hypertension, and pain management was awful," said Arnold Chan, Associate Professor at the Harvard School of Public Health (Cambridge, MA, USA). "Now we have more effective medicines, so the adverse event profile is becoming increasingly important. Indeed, a good safety profile is a strong selling point. The choice of a drug often no longer comes down to which is the most effective—there is often little to choose between similarly efficacious products. It's which is the safest."

Regulatory structures have not fully kept pace with this sea change: the design

of clinical trial programmes still emphasizes efficacy and detecting common side effects rather than picking up relatively rare, but clinically important, adverse events. Traditionally, clinical studies of new drugs take part in three phases. During phase I, between 20 and 80 people, usually healthy volunteers, take the drug to assess its safety and to establish pharmacokinetics and pharmacodynamics. Phase II studies typically enrol between 100 and 200 patients to confirm the safety profile and establish proof of principle that the drug will be effective for the proposed indication. Finally, phase III studies aim to show that the drug offers significant clinical benefit and an acceptable adverse-event profile. The number of patients enrolled in a phase III study depends on the drug and the condition, but is typically between 200 and 2,000. In most cases, 30%–50% of the patients receive the new drug; the remainder receive a placebo or comparator.

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Partly to address growing safety concerns, regulatory authorities increasingly demand larger and more complex phase III studies. However, there is a limit to how far regulators can push the current structure. Chan commented that regulators must balance the need to ensure drug safety with the need to promote innovation

and investment in pharmaceutical research and development. Demanding larger or more sophisticated studies increases costs, which would make research in many therapeutic areas too expensive, while larger studies may still be unable to anticipate all possible adverse effects.

Conversely, pharmaceutical companies could do more to ensure they fully leverage current programmes. "If phase III studies detect a potential elevated risk of an adverse event even in a small number of patients, a number of steps should be taken to increase the likelihood of approval and decrease the chances of subsequent withdrawal," said Richard Gliklich, CEO of Outcome (Cambridge, MA, USA), a company that provides electronic post-approval studies, registries and risk-management programmes. "Primarily for the sponsor, a risk-management action plan is needed to address potential concerns. Even before launch, a sponsor can start a registry to develop primary background safety data in the population with the disease." Gliklich suggests, for example, that companies could propose phase IV and other studies, implement a safety registry and control distribution—for example, to certain patients or clinicians only. In several countries, this is already a reality; patients suffering from rheumatoid arthritis and other inflammatory diseases who take monoclonal antibodies and other biological agents targeted against tumour-necrosis factor- α are registered in databases. Similarly, patients taking the

antipsychotic drug clozapine—an effective treatment for schizophrenia that carries a risk of blood disorders—are enrolled in a monitoring programme.

Nevertheless, clinicians and regulators need to extrapolate from, at best, several thousand patients who received the medicine in clinical trials to the many millions who may take the drug once it is on the market. This expansion in exposure means that unexpected side effects often emerge only after approval. "If you think of a normal curve, once the drug is in general use, patients at the tail ends of the distribution curve are far more likely to get the drug," Gliklich said. Moreover, clinical studies of drugs for chronic diseases may last for months, whereas patients take the drug for years. The inclusion and exclusion criteria of a study also often do not reflect the patient population in naturalistic practice because the trial design aims to avoid the potentially confounding effect of concurrent drugs and diseases as well as reducing the risk to patients by excluding, for example, elderly patients. In the real world, however, concurrent diseases and polypharmacy are common, and doctors prescribe many drugs to a wider age range than that enrolled in the study. Against this background, Eric Topol, Provost at the Cleveland Clinic Lerner College of Medicine and Professor of Medicine and Genetics at Case Western Reserve University (Cleveland, OH, USA), commented that "It is absolutely essential to

perform a systematic safety review once the drug is marketed to look for unexpected adverse events."

Ironically, Vioxx's pivotal study was large for a phase III study, involving 8,076 patients. Nevertheless, it was not powerful enough to reliably detect rare adverse events with a prevalence of 1%–2% compared with placebo, which eventually led to Merck withdrawing the drug. And, ironically, a study with stringent inclusion and exclusion criteria had a major role in Vioxx's withdrawal. The APPROVe (Adenomatous Polyp Prevention on Vioxx) study aimed to determine if rofecoxib prevented the malignant transformation of colon polyps and excluded patients with heart disease. Over the first 18 months, APPROVe did not link Vioxx with an increased risk of cardiovascular events. However, 3.5% of patients taking rofecoxib for more than 18 months suffered either a myocardial infarction or stroke, compared with 1.9% in the placebo group—an excess risk of 16 infarcts or strokes per 1,000 people taking the drug. During the 5.5 years it was on the market, more than 80 million people were prescribed Vioxx (Topol, 2004; Frantz, 2005).

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During US Senate hearings into the Vioxx withdrawal, an FDA drug-safety expert called for several other drugs to be pulled from the market because of what he considered to be unacceptable adverse events: Accutane® (Roaccutane®; isotretinoin) to treat acne; Bextra® (valdecoxib), a COX-2 inhibitor; Crestor® (rosuvastatin), which lowers cholesterol; Meridia® (Reductil®; sibutramine) for obesity; and Serevent® (salmeterol) to treat asthma. The FDA stressed that these were personal views and the companies defended the safety of their drugs (Anonymous, 2004). Whatever the pros and cons, these controversial comments underscore the need to place the decision to withdraw a drug into objective hands.

In Europe, for example, regulators monitor safety during a rolling five-year window and the drug is re-reviewed five years after approval (Frantz, 2005). There have been calls in the USA to instigate similar initiatives (Anonymous, 2004). At present, the FDA can ask a company to perform a phase IV study and, indeed, have requested an increasing number of phase IV studies over recent years. However, the company is under no legal requirement to do so, and most of these studies are never performed, according to Topol. "The FDA should have the legal authority to require a company to perform these studies," he argued, adding that there should also be no direct-to-consumer advertising and promotion until post-marketing surveillance validates the safety of the drug. Topol also called for regulatory authorities to ensure that companies publish the results of all their clinical studies in online databases.

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Some experts want to go further and grant 'provisional' product licences. Chan favours a system that conditionally approves a drug for a defined period, such as five years. The authority would then re-review the agent to evaluate its risk-benefit profile after post-marketing use. "A probationary period balances the

pre-marketing requirement and post-marketing public-health protection," he said. He suggested that the regulatory authority and the company agree on the duration of the phase IV studies, the number of patients enrolled, the outcomes and so forth. "Post-marketing studies could be minimal, or substantial, but should be driven by science," Chan added. For example, regulatory authorities may need more rigorous studies when a drug is first in a class or meets a previously unmet need. Gliklich agreed: "Contingent approvals with limited early distribution of certain drugs may be a good way to balance competing goals of making drugs available swiftly while maximizing long-term safety."

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Several other changes could also help prevent drug withdrawals. Topol, for instance, would like to see companies "let go" of their clinical trials and allow academics to lead the studies. This would better define the adverse-event profile by performing scientifically definitive studies, and would augment transparency. In the future, pharmacogenomics may also help researchers to hone the risk-benefit analysis in detecting polymorphisms that cause adverse events, as Topol commented: heart attacks and strokes in Vioxx users, liver toxicity associated with the direct thrombin inhibitor Exanta® (ximelagatran) and side effects among adolescents linked to selective serotonin reuptake inhibitors, which are used for depression and other psychiatric disorders. Chan also suggested that pharmacoepidemiologists could make greater use of data from disparate sources, including observational studies, genomic analyses as well as retail and hospital pharmacies.

Finally, Chan called for a change in doctors' attitudes as clinicians are notoriously poor at reporting adverse events (Eland *et al*, 1999). He commented that the increasing focus on patient-centred care means that time-pressured doctors attach a relatively low importance to broader public-health issues. In addition, when doctors contact pharmaceutical companies—who are obliged to report

adverse events—it is often in the context of asking for advice rather than reporting side effects *per se*. Chan therefore believes that the clinical care delivery system needs a structural change in the assessment and reporting of side effects that is akin to the intellectual basis, if not the legal foundation, of notifiable infectious diseases.

At first sight, such measures—instigating phase IV studies and bolstering other pharmaco-epidemiological approaches—could further drive up R&D costs. Current estimates suggest that these costs have already reached about US\$1 billion (DiMasi *et al*, 2003), a level of expenditure that could make drug development unsustainable for companies and medicine unaffordable for patients (Rawlins, 2004). Nevertheless, greater vigilance would be in everyone's best interest—even pharmaceutical companies. "There is nothing more costly than the withdrawal of a drug," Gliklich said. "Pharmaceutical companies, regulatory agencies, doctors and patients are all aligned in trying to minimize risk." The FDA recently announced a major review of its systems for monitoring marketed drugs. Time will tell if this reduces the number of drug withdrawals and helps to reassure patients and clinicians that their medicines have the best possible risk-benefit ratio.

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