EDITORIAL

RISKY BUSINESS

The need to establish improved drug-safety detection measures after the withdrawal of Vioxx is paramount, but setting up such systems will be far from easy.

Risk is a concept that the pharmaceutical industry has long been familiar with. The level of attrition associated with all stages of discovery and development makes the search for innovative drugs risky and expensive. But the high-profile withdrawal of Vioxx (rofecoxib; Merck) a year ago due to cardiovascular adverse effects detected in patients with colon cancer generated an altogether different level of risk awareness. Although Vioxx has re-taught many people that the approval and use of drugs are based on evaluating risk versus benefit, the circumstances leading to the drug's withdrawal has prompted many questions regarding the integrity and future of the pharmaceutical industry.

In light of the many issues raised and debated over the past year, what lessons can be learnt from the saga of the COX2 inhibitors to help the industry move forward? On page 800 in this issue, ten leading researchers involved with the development and use of the COX2-selective inhibitors provide their unique insight into this matter, and the diversity of responses provides a telling sign of the task ahead. A recurring theme is that the risk of a drug cannot be fully evaluated before it is approved, and that the collective ability to monitor drugs once they are on the market is poor. The current system of spontaneous reporting of any adverse effects of a drug on the market works well if the risk is rare, as in the case of progressive multifocal leukoencephalopathy with Tysabri (natalizumab; Biogen Idec/Elan), because even a couple of cases stand out against the background patient population. But with an event that is already common in the treatment population, and occurs at a level of around 1.5 per 100 patient years — both of which applied to the cardiovascular events with Vioxx — companies, physicians and patients have found to their cost that there is no adequate system in place to detect such an adverse risk.

The fact that a risk such as found with Vioxx can only be picked up once a drug is on the market and prescribed to tens or hundreds of thousands of patients has forced companies to reconsider their safety-monitoring strategies, and the way they establish adequate risk-management plans. The idea that any potential adverse signal be followed and explained before filing a drug for approval or during post-market surveillance sounds straight-forward on paper. In practice, however, proving a signal is related to an adverse effect of a drug is a difficult task, not least because the evidence-based standard that companies should use to issue warnings about the safety of their drugs is not clear. Analysing populations of unhealthy people taking one or more treatments presents a complex problem, as any signal could be due to the illness, the drug or an unrelated factor. And what type of signal constitutes an acceptable risk varies with the problem, drugs and the condition being treated.

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The need for good IT infrastructure is therefore crucial, as capturing all this information from clinical trials to guide the intepretation of adverse signals is a mind-boggling effort. Companies have to integrate information from trial protocols, patient records, clinical records, adverse event reports and, where available, genomics data. Often, drug-safety monitoring processes and the wealth of data that stream from them are scattered throughout an organization, although, as shown on page 806 in this issue, some companies have successfully centralized their pharmacovigilance departments.

However, a recent report from Life Science Insights states that the pharmacovigilance applications and services available to support and manage drug-safety monitoring are not maturing at the same pace as the current demand. Given this, perhaps we should be looking to maximize the experience from existing, academic pharmaco-epidemiology departments to carry out observational studies in drugs. Such groups have access to databases with millions of patient records and can track people over any period of time. For instance, FDA's David Graham's statement that there were an estimated 88,000–140,000 excess cases of serious coronary heart disease while Vioxx was on the market came from retrospective medical claims data from Kaiser Permanente, a managed care organization in the United States (Graham, D. J. *et al. Lancet* 365, 475–481; 2005). This approach does have certain limitations, but the resources and the expertise are there to pick up adverse signals if people are willing to use them. At a time when all aspects of drug safety are under surveillance, the industry needs to pursue all options to make sure it avoids another catastrophe.