COMMENTARY

Re-examining our approach to the approval and use of new drugs

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In this issue, Bellini and colleagues report on a preterm infant who experienced pulmonary hypertension after receiving L-lysine ibuprofen therapy for patent ductus arteriosus.[1] Their case report is yet another reminder that therapies can have unforeseen adverse reactions, and it also highlights the importance of continued surveillance after a new therapy or technology is introduced. Rare adverse reactions are seldom detected by clinical trials, and they are usually only discovered years after the therapy has been adopted as routine care, as the number of patients receiving the drug increases. In many cases, the adverse drug reactions are not severe or life-threatening, and the issue never enters the public domain. Occasionally, however, the effects are highly injurious or life-threatening and patients are harmed, in which case the social, ethical and economic fallout following public disclosure can be severe and long-lasting. The recent Vioxx affair is a case in point. But how common are these adverse drug reactions, and how soon after a new drug is introduced are they usually detected? Lasser and colleagues[2] recently reported that of 548 new drugs approved by the US Food and Drug Administration (FDA) between 1975 and 1999, 56 (10.2%) acquired a black box warning and 16 (2.9%) were withdrawn from the market. This translates into a 20% probability of a new drug acquiring a black box warning or being withdrawn from the market over a 25-year period. Half of these warnings and withdrawals occurred within 7 years of the drug's introduction, and half of the withdrawals occurred within 2 years. These data show that serious adverse drug reactions occurring after FDA approval are not uncommon and should be a cause for concern.

Lasser and colleagues[2] point out that there are numerous reasons for the late detection of these adverse drug reactions. Many premarketing clinical drug trials are underpowered to detect adverse drug reactions.[3] In some cases, approvals have been granted even when adverse drug reactions were detected by premarketing clinical trials; for example, alosetron hydrochloride was reported to be associated with ischemic colitis.[4] Follow-up studies are often lacking, and some drug companies fail to conduct postmarketing (Phase IV) studies, which are required when a safety question arises during the preapproval process. Pharmaceutical companies actively promote early use of new drugs and seek to influence physicians' prescribing patterns and patient preferences through direct-to-consumer marketing so that they can rapidly increase sales and change prescribing patterns ahead of competitors.[5–7] Market-driven concerns about patent life, profitability and investor stock prices provide strong incentives for these behaviours.[8]

So how should doctors, patients and regulatory bodies respond to the problem of adverse drug reactions? First, doctors should avoid using new drugs when older, reliable alternatives are available. Second, patients should be informed of the limited safety data on new drugs and be advised to be alert for possible adverse reactions. Third, labelling for all new drugs should include the approval date and a black box warning about limited safety data. Fourth, possible adverse drug reactions should be reported to a regulatory agency or voluntary body such as MedWatch and the information disseminated to clinicians. Fifth, a surveillance system operated under the auspices of regulatory agencies should be required for all new drugs. Finally, the regulatory threshold for the approval of new drugs should be higher if there are safe and efficacious alternatives already in existence. Given the magnitude of the problem and the danger to public health, it is imperative that these measures be implemented as soon as possible, and that the public be made aware of the dangers associated with using new drugs.

This article has been peer reviewed.

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Competing interests: None declared.

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DOI:10.1503/cmaj.060581