EDITORIAL

The hazards of rapid approval of new drugs

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The approval of new drugs is a complicated and sometimes controversial process. Even the US Food and Drug Administration (FDA), one of the largest regulatory agencies, sometimes makes mistakes. These are often related to its 'fast-track' options, which aim to quickly approve new drugs for serious illnesses. However, approval can be made too early for drugs with limited data or data reliant on biochemical surrogate markers.[1] There is less chance of identifying adverse drug reactions before marketing for drugs that undergo fast-track approval.[2]

Canada has also developed a fast-track process and a recent analysis found that safety warnings are significantly more likely after this process than they are with drugs approved through the usual regulatory process. Between 1998 and 2013, 27 drugs were approved on limited data and 11 (41%) subsequently received a safety warning or were withdrawn because of safety concerns. In the same period there were warnings or withdrawals for 50 (19%) of the 265 drugs approved after a standard evaluation.[3]

In spite of these concerns, at the end of 2014 the Australian Government called for measures to 'cut red tape' – proposing that the Australian Therapeutic Goods Administration (TGA) accept 'trusted international standards'. 'This will remove regulatory duplication, reduce costs and delays for businesses and consumers, increase the supply of products into the Australian market and allow regulatory authorities to focus on higher priorities.' The first step will enable manufacturers of medical devices to use certification by the European Union in place of TGA certification.[4]

While this reform sounds laudable, the TGA safeguards and enhances the health of the Australian community. This consists of a population of different ethnic backgrounds and different comorbidities, which affect the pharmacokinetics and pharmacodynamics of drugs. Australian prescribing practices and treatment algorithms can also be different so the results of overseas trials may not be applicable to Australian practice. In the evaluation process, the TGA can currently request the drug's manufacturer to provide justification as to how the drug is either known to, or likely to, behave in Australian clinical practice.

The Government did not consult any clinical expert groups and seemingly ignored the overseas concerns when making its proposal. It did belatedly ask for submissions on a strategy document in December 2014 with a deadline of 5 January 2015. We were involved in preparing responses critiquing the proposal on behalf of the Royal Australasian College of Physicians and the Australasian Society of Clinical and Experimental Pharmacologists and Toxicologists.

Prescribers should be aware of some of the examples where inadequate information at the time of rapid registration has been followed by significant adverse reactions, which have resulted in the drug being removed from the market.

One of the most widely known cases in Australia was rofecoxib, which was withdrawn because of serious cardiovascular adverse events. Despite a senior medical officer of the FDA noting a threefold increase in cardiovascular problems, the FDA gave rofecoxib priority status. Millions of people took the drug and worldwide sales totalled US$2.5 billion in 2003 alone. However, within months of the approval, a trial reported a doubling of heart attacks and strokes. In the USA, it was estimated that an excess of up to 139 000 people suffered a heart attack or stroke, and up to 40% of those died before rofecoxib was recalled.[5]

Ponatinib is a drug for chronic myeloid leukaemia that was assessed via the FDA's accelerated-approval pathway. This aims to expedite registration to address an 'unmet medical need', that is 'providing a therapy where none exists or providing a therapy which may be potentially better than available therapy'.[6,7] Ponatinib approval was based on data from a single

From the Editor

Gastro-oesophageal reflux disease is a common problem. Charlotte Keung and Geoffrey Hebbard review its management. At the other end of the gastrointestinal tract, Steven Schlichtemeier and Alexander Engel advise on the treatment of anal fissure.

With the increasing prevalence of kidney disease there is a greater need to be aware of drugs that are affected by renal function. Brendan Smyth, Ceridwen Jones and John Saunders discuss prescribing for patients on dialysis.

Reductions in renal function can result in toxic concentrations of digoxin. Matthew Pincus provides advice on how to manage digoxin toxicity.

Opioid toxicity is used by Sara Bird as an example of the risks of giving drugs to close acquaintances. She warns on the pitfalls of prescribing for family and friends.

There are also pitfalls in bringing new drugs to the market. Jennifer Martin and Gillian Shenfield alert us to the hazards of rapid approval of new drugs.

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phase II study of 449 patients with a median follow-up of 10 months. This study had only historical controls and was unblinded. With such minimal data one would expect robustly demonstrated outcomes to justify approval. In fact no patient-relevant outcomes such as overall survival or quality of life were used. Efficacy was accepted on non-blinded, non-randomised comparative data about the surrogate outcome of major cytogenetic response.[8] Ponatinib was subsequently removed from the US market because nearly half the patients had adverse vascular effects, such as venous thromboembolism, at three years.[1] With more data at an earlier stage ponatinib may never have been approved. It has now been marketed in Australia with a black box warning about its potentially fatal adverse effects.

Dabigatran has been associated with severe bleeding and it has emerged that the manufacturer withheld some information about how to use the drug safely and the FDA ignored advice from a majority of its advisory committee. This resulted in the approval of doses (150 mg twice daily) that were too high for some patients.[9,10] Australians were spared some of these problems as the TGA was more cautious than the FDA and recommended a lower dose (110 mg twice daily) for patients at risk of bleeding, such as those with renal impairment.

There have been many other drugs that have come under the rapid review processes of the FDA. Examples of problems not seen when the initial marketing approval was given, usually due to small numbers of patients and short-term use, include sofosbuvir causing serious bradycardia and deaths when used with amiodarone,[11] dimethyl fumarate and the risk of progressive multifocal leukoencephalopathy,[12] and troglitazone causing acute liver failure, the need for transplants, and 94 deaths.[13] Priority review status has also been given to drugs that treat non-life-threatening diseases, for example alosetron for irritable bowel syndrome in 1999. This drug caused at least four fatalities and severe adverse effects requiring surgery. It was withdrawn in 2000, within a year of its launch, but was reintroduced in 2002 with restrictions on its use.

We conclude that, as well as the problems with safety in small and short-term studies, the use of biomarkers (as opposed to actual clinical outcomes) in the rapid review process is often insufficient for a safe assessment. A slower and more comprehensive consideration of adverse events in well-conducted trials might temporarily deny a few patients an effective treatment but save the lives of many more. The FDA is a highly respected organisation and of course makes many correct decisions that are very helpful to other countries, but it does not get everything right. The same is true of all drug regulatory agencies including the TGA. The TGA is currently interested in the fast-track option and appointed a working party of three (without a clinical pharmacologist) to review the suggestion. Their first statement recommended fast tracking as one of three parallel routes and is being discussed currently at workshops which include all interested parties.

Although small efficiencies may be possible, the Australian population has been well served by the TGA in its current form. We consider the Government's attempt to speed up drug registration approvals by reducing, or perhaps ceasing, the TGA's role could be detrimental for the appropriateness and safety of new medicines in Australia.

Jennifer Martin provides consulting advice to the TGA.

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