

Fast-tracking of new drugs: getting the balance right

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In Australia, like the rest of the world, patients and their doctors have a growing desire to access new drugs as soon as possible. They hope to make an impact on conditions with limited pharmacotherapeutic options, such as cystic fibrosis and rare cancers like mesothelioma. New approaches to more common diseases, such as lung cancer and dementia, may offer greater efficacy or less toxicity than current therapies. The pharmaceutical industry is also hungry for expedited drug approvals as a vehicle to reward and encourage innovation. Faster approvals may increase company profits as products get to the market more rapidly.

In 2015, new drug approvals in Australia by the Therapeutic Goods Administration (TGA) took a median of 391 days from application, which compares favourably with Europe at 478 days.¹ However, the US Food and Drug Administration (FDA) approves new drug applications faster than any other country at a median of 304 days. There is a paucity of published data in any jurisdiction on how any accelerated drug approval mechanism reduces the time frame for availability compared to traditional evaluation processes. The FDA aims to review a priority application within six months as opposed to 10 months under standard review.

The approval of new drugs is an increasingly complicated process. Clinical trial designs and procedures have become progressively more complex. Furthermore, the proliferation of biological therapies (including biosimilar medicines) compared to traditional small-molecule drugs has added layers of intricacy to the evaluation process. As such, a traditional drug regulatory framework may no longer be the most appropriate assessment process for dealing with quickly evolving scientific advances.

The traditional approach in the assessment of a new drug involves a sequence of clinical trials (phase I–III). Accumulated evidence of dose justification, efficacy and safety in specified treatment indications and target populations then enables the drug's sponsor to apply for registration of the drug. However, in the last 20 years, several regulatory bodies have tried to develop and test fast-track approval processes for drugs to treat severe diseases for which the options are limited.

Following a review¹ the TGA consulted about expedited approvals² and has introduced a priority review pathway. This aims to assess new drugs within 150 days.³ The European Medicines Agency (EMA) introduced its PRIME (Priority Medicines) program of accelerated approval

and priority review in 2016. The FDA already had such programs, and in 2017 new molecule drug approvals were at a 20-year record of 46 (more than double the 22 approved in 2016). Of the 46 new molecular entities, 18 (more than half for oncology indications) received approval through the fast-track pathway.⁴

In these programs drugs for serious illnesses are rapidly approved on the basis of limited clinical trial data or data reliant on surrogate outcome measures, some of which are biochemical, for example glycated haemoglobin (HbA1c), rather than clinical. Anticancer drugs may be approved on response rates, often measured over relatively short time frames, rather than on improved survival. Between 2009 and 2013, the EMA approved the use of 48 oncology drugs for 68 treatment indications, eight of which were approved on the basis of a single-arm trial.⁵ An analysis of the data reports that in approximately half (35 of 68) of the indications there was a significant improvement in survival or quality of life, whereas in the other half, the benefit remained uncertain.

Advocates of rapid access to new therapies claim that targeted treatments such as modern immunotherapies do not fit current regulatory processes. With an enhanced contemporary understanding of disease pathogenesis pre-study, novel immuno-oncology drugs are clinically tested in trials with small patient numbers and often in the setting of knowing the patient's genetic profile. It is claimed that these attributes allow for better prediction of response with fewer significant adverse events. Furthermore, advances in digital technology, remote monitoring, patient sensors and data analytics are allowing for improved recording of reliable and validated patient-related outcomes in studies with smaller sample sizes. Critics of faster access to new drugs are concerned that it comes at the expense of patient safety and increases the financial risks for the individual and society.⁶ Moreover, the acceptance of overseas regulatory decisions to facilitate rapid drug approval in another country is frequently complicated by significantly different assessment criteria across the major jurisdictions. There are also distinctive differences in clinical practice, making the extrapolation of regulatory decisions to other countries potentially hazardous.⁷

Canadian (1998–2013) and US (2001–10) experience with expedited approval processes showed that fast-tracked drugs were twice as likely to be subsequently withdrawn

from the market or to receive major safety warnings compared to drugs approved by standard processes. Analysis of the FDA fast-track data found that it took a median of 4.2 years after a drug's initial approval for major safety concerns (including death) to come to light. Postmarketing problems were more common for psychiatric drugs and biological therapies.⁸

A challenge for drug regulators is that many new drugs granted accelerated consideration are often not the first in their class as nowadays several companies may work on the same drug targets (e.g. programmed death ligand therapies). In 2017, only one-third (15/46) of accelerated new drug approvals in the US were first-in-class therapies, compared with up to 50% in 2012.⁴ In addition, many of the drugs spiking interest for rapid access are targeted immunotherapies that may have the potential to be used across multiple treatment indications, in the same way that rituximab can be used to treat various autoimmune diseases and cancers. Across the globe, many regulators have published guidelines on the eligibility criteria and processes for managing expedited drug approval, but there is a lack of clarity on the post-authorisation handling of safety and efficacy failures following accelerated approval.

In March 2018, the TGA announced a provisional approval pathway. This will allow drugs to be available for up to six years based on preliminary data.⁹ The anticancer drug olaratumab is the first drug to be considered for provisional approval in Australia.

Access to new therapies is a balance between evidence (determining the risk of acceptable adverse effects versus efficacy) and the speed of availability, intersected by the issue of affordability. Making a drug available early with temporary authorisation is

not a new concept, particularly for patients with life-threatening or seriously disabling conditions for which there is a clear unmet therapeutic need. Temporary access is akin to a learner driver receiving their provisional licence – a full licence is only granted after more experience. Rapidly approved drugs should receive provisional registration for a period of three years and the drug company should be required to provide annual data on the postmarketing experience.

In Australia at present, sponsor companies are required to report all negative outcomes that they become aware of, but there is no imperative for them to actively and meticulously seek out adverse events, or confirm efficacy after approval. As pharmacovigilance relies on spontaneous voluntary reporting of adverse effects by clinicians, it is highly likely that safety concerns are under-reported.

Improving the scientific rigor of postmarketing information to track effectiveness and safety outcomes, either through independently monitored registry studies as a condition of initial registration or data linkage (e.g. with linking of Pharmaceutical Benefits Scheme and Medicare Benefits Scheme datasets), will be of paramount importance during any provisional registration period. If efficacy outcomes in the real-world environment are not confirmed or a significant safety problem emerges, then the drug's registration should be suspended, at least for previously untreated patients, until the sponsor satisfactorily addresses the problems. ◀

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