Regulatory reforms in Australia – improving access to new medicines

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Abstract
The Australian medicines regulator, the Therapeutic Goods Administration (TGA), is concerned about a general lag of application submissions compared with those in the US and the EU. In this article we investigate the TGA's Comparable Overseas Regulator (COR) approval pathway and further developments in work-sharing arrangements, which are aimed at building closer connections with other regulators to explore reducing the participating agencies' respective workloads for an overall improvement in drug development and evaluation. This will ultimately lead to earlier access to life-saving medicines for patients.

As a medium-sized regulator, the Australian Therapeutic Goods Administration (TGA) is aware that the number of new chemical entity (NCE) submissions received are lower than the submissions made to the US FDA and the European Medicines Agency (EMA); one in three new medicines evaluated by the TGA are approved by the FDA before an application is even submitted to the TGA. A similar lag is noted in comparison with EU product assessment since submissions to the EMA are generally made simultaneously with the FDA.[1] The TGA submission gap with the FDA has grown significantly in recent years, with the median gap from FDA submission to TGA submission having doubled in 2017 to 499 days, compared with 196 days and 233 days in 2015 and 2016, respectively.

The TGA would like to understand the cause of this lag and why the submission lag is increasing: why do sponsors obtain approval in the US and EU before submissions to the TGA and what changes can be made to the TGA regulatory framework to encourage applications to the TGA at the same time as they are submitted in the US and EU and, at a minimum, to reduce the potential for submission lag between the markets.

One possible explanation is that global sponsors choose to submit dossiers to the largest regulators first to avoid dealing with several sets of questions simultaneously. There can also be therapeutic-use differences between the submissions in Australia and those to other regulators. While regulatory reforms offer solutions to a reduction in the submission lag, it is also possible that the TGA's eventual implementation of full electronic common technical document (eCTD) submission requirements to bring them in line with other regulators will also help to minimise this lag. In October 2018, the TGA released a consultation to industry for a proposed model of transitioning to acceptance of eCTD formatted dossiers only for prescription medicine approval.[2]

The approval pathways

Since 2016, the TGA has been implementing several regulatory reforms in response to recommendations from an expert panel, which conducted the 2014 Review of the Medicines and Medical Devices Regulation (MMDR).[3] The aim of these measures is to streamline the TGA's assessment and registration processes and improve timely access to medicines for Australian consumers.

In 2018, the TGA formally introduced several regulatory reforms aimed at further improving access to medicines and the renovation of the regulatory process, following strong industry and patient calls for new approval pathways. Two current initiatives are: a Comparable Overseas Regulator (COR) pathway that enables sponsors to use approval in other markets to speed up the evaluation process; and work sharing with other regulators of similar size to the TGA.

The Comparative Overseas Regulator

The TGA first considered which overseas regulators they were willing to rely on to improve evaluation timelines using overseas evaluation reports, via establishment of these identification criteria:

- Whether the regulator conducts pre- and post-marketing activities
- Whether there is a formal memorandum of understanding between the overseas regulator and the TGA
- Whether the regulator has adopted international guidelines and standards consistent with those used by the TGA
- Can the overseas regulator provide reports and communicate in English?

Following an assessment of regulators against the COR criteria, the initial list of comparable regulators included Health Canada, Health Science Authority Singapore, Swissmedic, the UK Medicines and Healthcare products Regulatory Agency, the FDA and the EMA.

The COR pathways

Before the introduction of the COR reliance in January 2018, the TGA had a single standard pathway for all new medicines, with an evaluation timeframe of around 200–250 working days. The TGA has now introduced two approaches for the COR approval pathway. The application and evaluation fees for the applications submitted under the COR-A or COR-B procedure remain the same as a full application.

The COR-A pathway, a 120-working day process, requires that the medicine and the manufacturing sites submitted to Australia are identical to the product approved overseas, and that the dossier is submitted with satisfactory evidence of good manufacturing practices. The overseas marketing approval that it is dependent upon must be no older than one year and no additional evaluation

of data must be required for Australia, other than labels, Australian-specific product information and consumer medicine information documents.

The COR-B pathway, a 175-working day process, is still based on reviews of overseas evaluation reports but additional data may be reviewed by the TGA. The additional data may include updated stability data, validation data for an additional manufacturing site and updated pivotal clinical studies or new safety data.

The new COR pathways require a degree of cultural change and trust from the TGA. In particular, the TGA's confidence in assessments by evaluators at other regulators is critical to the acceptance of overseas evaluation reports.

TGA work-sharing pilot update

The TGA work-sharing initiatives were derived from the MMDR reviews, which recommended that the TGA better utilise opportunities to workshare with comparable regulators. The review of work sharing was aimed at improving efficiencies in the review processes and developing streamlined entry for applicants into multiple international markets, ultimately enabling earlier access to medicines for Australian consumers by reducing the submission gap.

Recognising the shared challenges facing medium-sized regulators such as the TGA, particularly ensuring access to safe medicines with limited resources, a working group was formed between the regulators to develop opportunities for greater alignment of regulatory approaches and technical requirements. The working group, known as the ACSS (Australia, Canada, Singapore, Switzerland) Consortium[4], was established in 2012. The purpose of the ACSS is to promote greater regulatory collaboration between like-minded, medium-sized international regulators across multiple areas.

Through this initiative, a work-sharing pilot was established to compare the coordinated assessment of an NCE application that had been filed in two of the pilot jurisdictions.

A highlight of the work-sharing initiative, which demonstrated the associated benefits, was the priority evaluation assessment of apalutamide. The assessment was the first work-sharing initiative between Health Canada and the TGA (HSA [Singapore] and Swissmedic were observers). The TGA provided a partial clinical evaluation (clinical pharmacology, bioequivalence and pharmacokinetic) and a full toxicology assessment; Health Canada performed the full clinical and quality evaluation – integrating the clinical evaluations between Health Canada and the TGA. During evaluation, there were multiple teleconferences between agencies to discuss relevant issues; rolling questions and sponsor responses to questions were shared between the parties. After the evaluation, there were separate product information and labelling negotiations with local sponsors in Canada and Australia, with the final decision provided within 80 working days. The assessment led to the first medicine to be registered in Australia under the ACSS NCE work-sharing pilot.[5]

Work-sharing procedure overview

Potential sponsors who wish to consider the advantage of the work-sharing arrangement should contact the TGA at least three months — and up to six months — before a planned submission.[6] Sponsors should consider the best regulatory pathway for the submission; for example, whether priority or orphan designations will apply. Following the expression of interest in participating in the work-sharing pilot, the TGA will then approach the nominated CORs to discuss their involvement on behalf of the sponsor.

Before the introduction of the COR reliance in January 2018, the TGA had a single standard pathway for all new medicines, with an evaluation timeframe of around 200–250 working days. The TGA has now introduced two approaches for the COR approval pathway, both of which have shorter evaluation timeframes

Three months prior to submission, the product sponsor will commence pre-submission meetings with regulators. A three-way meeting between the sponsor and participating regulators is possible. The regulators and sponsors will clarify any differences in dossier requirements for the participating regulators, synchronise submission dates and share reports with the CORs. A draft process and timeline will then be developed based on the relevant pathways and available agency resources, which is then shared with the sponsor.

At the time of dossier submission, negotiations with sponsors regarding evaluation questions (whether batched or rolling), evaluation timelines and milestones are confirmed. At that point, a sponsor communication plan is developed and the communication strategy between the participating regulatory agencies is agreed.

During the product evaluation phase, the regulatory agencies involved will share the evaluation reports as agreed between the parties. The agency evaluators and decision delegates involved will meet to discuss the data. To improve efficiencies, consolidated questions and sponsor responses will be shared across all parties. When it is time for a decision to be made, each agency will make its own sovereign decision regarding the product. If approved, simultaneous market authorisation can occur across all jurisdictions. Post-decision, the national product information (labelling), post-marketing negotiations and risk management plans will be developed separately with individual agencies and local sponsor entities.

Benefits of work sharing

The TGA believes a future expansion of the work-sharing initiative to include other national regulators will have many benefits to industry stakeholders both in Australia and globally. For sponsors, this benefit could include the potential for a decrease in the regulatory workload via a single-window evaluation procedure across multiple regulators, a flexible approach to the evaluation and approval process with regard to transparency and coordination, and the potential for simultaneous authorisation in all jurisdictions. For regulators, possible benefits include the ability to share expertise across several regulatory agencies, providing improved efficiencies owing to larger personnel availability, and the potential to reduce the regulatory effort required to approve a product while maintaining independent sovereign decision-making authority.

However, fees for the work-sharing arrangement will remain the same as those for a standard submission. The TGA has advised that "the NCE work sharing is still in the trial/pilot phase and at this stage has a focus on reducing regulatory burden (eg, with the filing of common dossiers), concurrent market authorisation decisions, and the opportunity to contribute to advancing regulatory innovation. While the TGA works through the practicalities of undertaking a single assessment that will support regulatory decision-making within each jurisdiction, it is difficult to estimate the extent to which this would result in a reduction in overall TGA evaluation effort. As such, the TGA has maintained the current prescription medicine application and evaluation fees. However, the valuable knowledge and experience being obtained through this work-sharing pilot will continue to inform internal procedures and workflows."

Currently, the work-sharing initiative is only available for specific applications and under certain conditions. Sponsors wishing to participate are invited to contact their national or regional regulatory authority in one of the four ACSS member countries.

The TGA has released its International Engagement Strategy: Operations Plan 2018–19.[7] The COR and work-sharing initiatives highlighted in this article are components of the overall goal to provide Australian patients with earlier access to medicines and medical devices while minimising the costs to industry.

References

1. Centre for Innovation in Regulatory Science. 'R&D Briefing 67. New drug approvals in six major authorities 2008 – 2017: Focus on the availability of medicines and company size'. London, UK. 2018. Available at: http://www.cirsci.org/wp-content/uploads/2018/05/CIRS-RD-Briefing-67-04052018_FINAL.pdf (accessed 23 November 2018).
2. Therapeutic Goods Administration. 'Consultation: Transition to eCTD only for prescription medicines'. Available at: https://www.tga.gov.au/consultation/consultation-transition-ectd-only-prescription-medicines (accessed 23 November 2018).
3. The Department of Health. 'Expert review of medicines and medical devices regulation'. Available at: http://www.health.gov.au/internet/main/publishing.nsf/Content/Expert-Review-of-Medicines-and-Medical-Devices-Regulation (accessed 23 November 2018).
4. Therapeutic Goods Administration. 'Australia-Canada-Singapore-Switzerland (ACSS) Consortium'. Available at: https://www.tga.gov.au/australia-canada-singapore-switzerland-acss-consortium (accessed 23 November 2018).
5. Australian TGA. International work-sharing pilot – apalutamide (Erlyand). 5 July 2018. Available at: https://www.tga.gov.au/media-release/international-work-sharing-pilot-apalutamide-erlyand (accessed 27 November 2018).
6. Therapeutic Goods Administration. 'ACSS - NCE work-sharing pilot'. Available at: www.tga.gov.au/acss-nce-work-sharing-pilot (accessed 23 November 2018).
7. Therapeutic Goods Administration. 'TGA international engagement strategy: operations plan 2018-19'. Available at: https://www.tga.gov.au/publication/tga-international-engagement-strategy-operations-plan-2018-19 (accessed 23 November 2018).

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Topics subject to change.