

Review of Medicines and Medical Devices Regulation – Cancer Council/COSA recommendations to the Australian Government

Background

The current regulatory system to approve medicines and medical devices has served the cancer community well in making available high impact medicines, however it is not sufficiently sensitive to assess the complexity of many emerging cancer treatments, particularly for medicines intended to treat small patient populations (Deloitte, 2013).

All submissions to the Therapeutic Goods Administration (TGA) are assessed by scientific and clinical experts to ensure the benefits of a product outweigh any risk, such as potential toxic side effects of prolonged use. This risk assessment approach is intended to assure consumers that products they take are safe for their intended use, while still providing access to products that are essential to their health needs (TGA, 2014). Medicines with a high risk, classed as category Aust R, can still be made available if demonstrated benefits are considerable and are obtained only through prescription after consultation with a health practitioner (TGA, 2013). A higher level of evaluation of data relating to safety, manufacturing and efficacy is applied to Aust R category medicines. The Review of Medicines and Medical Devices Regulation provides an opportunity to revise requirements and processes so as to reduce regulatory burden on business while achieving the desired intent of ensuring that therapeutic products on the Australian market are safe, high quality and clinically effective (Sansom et al. 2014).

In cancer research and treatment, the best available evidence is rapidly evolving, along with trends in standard treatment and clinical practice. More efficient and streamlined processes, with the ability to expedite access to medicines of clinical significance, are urgently required.

The review provides an opportunity to remove or streamline regulatory requirements that are unnecessary, duplicative, ineffective or inefficient, without undermining the safety or quality of therapeutic goods available in Australia.

Response to terms of reference:

- a) Ensure there is an appropriate balance between risk and benefit in the regulation of prescription, over-the-counter, complementary medicines and medical devices**

Context in summary:

Evidence to support an application to the TGA requires the production of clinically meaningful outcomes through phase three randomised controlled trials, which can pose a significant barrier to evaluate drug efficacy in rare malignancies including subsets of cancer.

Cancer Council Australia/COSA discussion:

Under the Therapeutic Goods Act 1989, the TGA must assess a therapeutic good as demonstrating safety, quality and efficacy or performance before they can be lawfully imported, manufactured, supplied or exported in Australia (Australian Government, 2014). Access to high quality, safe medicines with proven efficacy are expectations that Australian health care consumers and the broader community have towards market available medicines. Delays in the registration process can result in delays in access by health care consumers to therapeutic products.

Overall survival is often considered to be the most clinically relevant and meaningful end point on which a drug's value is assessed, especially for medicines for the treatment of late stage cancer (Olver, 2013). Such evidence is comprehensively produced through a phase three randomised controlled clinical trial however, this research design is not always feasible in cancer research.

Where appropriate, additional endpoints, beyond direct overall survival, should be considered. This includes objective tumour response, response rate, time to progress, time to treatment failure, progression free survival (duration of time without disease progression) (Olver, 2013). The requirement to produce overall survival outcomes prolongs duration of trial, increases number of patients needed for recruitment and retention, increases cost of completing trial, increases confounding factors. In cancer research it can be particularly difficult to recruit and retain a patient study group large enough to produce significant outcomes.

In addition, advances in cancer research have generated a greater understanding of molecular biology, resulting in the identification of smaller subsets of cancer and, along with rare cancers, naturally produces small patient sizes (Olver, 2014). The use of surrogate endpoints which, still demonstrate major outcomes in benefit, would support the generation of clinically meaningful data in cancers with long survival, or generally present at a later stage.

Obtaining significant participant numbers to generate high quality clinical data to evaluate a drug's efficacy for rare malignancies or cancer groups treated with targeted therapies can be particularly difficult. In addition, the use of parallel-randomised controlled trials for cancer medicines is not always realistic as issues of crossover design can easily occur.

Cancer Council Australia/COSA draft summary recommendation:

Cancer Council Australia recommends that the Review Committee recognises, where appropriate, the merits of surrogate endpoints when making regulatory decisions, considering the risk and benefit relating to patient access to cancer medicines and medical devices.

a2) Ensure there is an appropriate balance between risk and benefit in the access for individuals to unapproved medicines and medical devices

Context in summary:

Unapproved medicines and medical devices are those not registered on the ARTG or are in use beyond the indications for which they were registered.

Cancer Council Australia/COSA discussion:

Currently, off-label prescribing is an integral part of patient care in cancer. Due to the aggressive nature of some cancers, prescribers may be more likely to consider off label drug use, especially for patients where all other registered treatment options have been

exhausted. The off label use of a medicine refers to its use outside of the terms of its registration by the TGA.

Off-label use of medicines brings with it a number of clinical, safety and ethical issues. However, for medicines registered on the ARTG but used beyond the approved indications, the opportunity to register additional indications would ensure that information about the use of the medicine or medical device is available to all health professionals and consumers.

A high rate of off label prescribing has been reported in cancer treatment as part of standard clinical practice. This represents a disparity between evidence based clinical guidelines for anti-cancer therapy and product approval. It can also create an inequality in patient care. Results of an audit of chemotherapy protocols and the presence of off label products being used in evidence based guidelines within a specialist cancer centre were published by Mellor et. al. in 2012. Of the 448 anti-cancer protocols in use, 42.9% contained at least one drug that was being used in an off-label or unlicensed indication, or in combination. They found that over 90% of off label products were supported by evidence based treatment guidelines or phase two or three clinical trials data. This inequality of access to appropriate medications for cancer patients in Australia is an issue.

The following reasons as to why TGA approved cancer medicines are being used beyond the indication/s for which they were approved have been identified:

1. Time delays due to the complexity of the TGA approval process, and only drug sponsors are permitted to lodge an application for a new indication. One of the express objects of the TGA, under section four of the Therapeutic Goods Act 1989, in addition to establishing a national system of controls relating to quality, safety and efficacy, is the timely availability of therapeutic goods (Australian Government, 2014).
2. Sponsors have no legislative requirement, obligation or incentive to lodge an application to register additional or changes to indications, or report new evidence or research discovery on a product once it is on the market. This has implications for prescribers and consumers using TGA approved products. In some cases, new evidence is developed by a research institution and not the treatment sponsor therefore data ownership from that research sits with the institution. In this case, the research institution cannot change a medicine's registration details, and as the data sits with the institution, restricts the sponsor from submitting evidence to broaden the indications;
3. It is difficult to obtain the required level of evidence to support application for approval especially in cancers which are rare or have smaller target groups;
4. The lengthy TGA approval process results in unacceptably long delays in the incorporation of clinical evidence into standard practice, guidelines or regulatory approval. It currently fails to support the timely incorporation of the most recently available evidence into practice and many TGA approved products do not have the most recent product information.

It is important that patients are protected from off label interventions that are risky and ineffective. While the incidence of off label prescribing is high, as Mellor et. al. (2012) demonstrates, the majority of off label chemotherapy prescribing is supported by established clinical guidelines or evidence from primary research reports.

The use of off label medicines has a particular impact on medicine affordability as the Pharmaceutical Benefits Advisory Committee (PBAC) only considers reimbursement if indication sought for reimbursement is consistent with TGA approval.

Addressing these issues may improve the responsiveness of the TGA registration status to changes in the cancer treatment and care.

Cancer Council Australia/COSA summary recommendation:

Cancer Council Australia/COSA recommends that the Review Committee recognises the prevalence of off-label prescribing of anti-cancer medicines in practice and considers the potential restrictions and reasons for these medicines' registration on the ARTG.

Term of reference:

b) Simplify and streamline the approval processes undertaken by TGA. This will include recommendations on:

i. fast tracking approvals processes for medicines and medical devices;

Context in summary:

Unlike other countries including the United States of America, cancer medicines to treat serious conditions and/or fulfil unmet need do not result in expedited registration.

Cancer Council Australia/COSA discussion:

There is increasing consumer demand for early access to novel therapies and sustainable access to effective treatment, especially for medicines and medical devices that are used to treat conditions where there is significant unmet clinical need; used to treat serious or life threatening conditions or; represent major advancement in treatment.

Although there is increasing demand from health practitioners and consumers for research outcomes to translate into market available medicines, the regulatory system must have capacity to appropriately balance the benefits of having early access to promising new treatments with the risks of access (Sansom et. al. 2014). Advances in technology and increased understanding of molecular biology have led to the introduction of many new cancer drugs, and the invention of targeted medicines and co-dependent technologies. The current regulatory system is currently not flexible enough to support this advancement and the demand for new products.

An expedited approval scheme would allow patients to gain access earlier to the most effective new medicines. The approval process would be required to be responsive and sufficiently rapid to allow patients likely to benefit from treatment to receive the medicine without lengthy delay. Expedited review could consider surrogate endpoints, such as disease free survival or change in a biological marker rather than clinical outcomes from a phase three trial. This evidence would support a medicine which has demonstrated clinical importance to enter the market early, with provisions around its ongoing availability (Cheng, 2013). Agreed future milestones could be monitored through regular post market assessment of efficacy through pre-determined reporting mechanisms. It would require a commitment from the sponsor to provide results of ongoing studies and greater monitoring of safety and efficacy post-market by the TGA.

In Australia sponsors can offer compassionate programs to approved patients, which provides them access to cancer medicines prior to registration on the ARTG. The Special Access Scheme is a pathway which provides early access however, this scheme is not a secure arrangement for the patient. Access via pathways such as compassionate access

programs do not provide sustainable and guaranteed ongoing access to non-TGA listed cancer medicines. Key issues include:

- arrangements for patient access is made by the clinician and sponsor;
- arrangement may not be equitable across all patients;
- sponsor may withdraw at any time
- disruptions to supply
- gaining approval may result in the particular indication/s being more restrictive, and no longer supports a broad range of indications used through the compassion programs

Cancer Council Australia/COSA summary recommendation:

Cancer Council Australia/COSA recommend further investigation into sustainable and equitable processes for expedited review and access to effective new or breakthrough medicines for patient groups who would benefit from quicker access to novel therapies; and consider conditions around the provisional approval of the drugs including consequences of not demonstrating clinical efficacy against pre-approved milestones, and implications for ongoing access for existing patients.

- ii. **opportunities for working together with trusted regulators in other jurisdictions, including the potential for work-sharing assessments for products marketed in multiple countries; and**

This is a complex area and requires review in its own right. Cancer Council/COSA will consult with colleagues/allies/supporters and advise.

(Note: On TOR (b)(ii) regarding opportunities for working together with trusted regulators in other jurisdictions, it is noted that the TGA participated in a pilot program for international cooperation, the final report of which was issued in 2011 (<https://www.tga.gov.au/improving-international-cooperation-between-regulators>). The current status of this project is unclear and its scope may be limited. Cross-border regulatory cooperation certainly takes place in other contexts, e.g. financial services.)

- iii. **exploring how risk assessments, standards and determinations of trusted regulators can be used more extensively by Australian regulators when approving the supply of medicines and medical devices.**

This is a complex area and requires review in its own right. Cancer Council/COSA will consult with colleagues/allies/supporters and advise.

Term of Reference:

- c) **Ensure regulatory arrangements are sufficiently flexible to accommodate developments in medicines and medical devices, including exploring opportunities to streamline approvals that cross regulatory categories;**

Context in summary:

Improve TGA responsiveness to clinical discovery and availability of up to date information relating to product and patient information.

Cancer Council Australia/COSA discussion:

Advances in technology and increased understanding of molecular biology have led to introduction of many new cancer drugs including the development of a large number of

molecular targets for novel anti-cancer medicines (Chim 2010, Deloitte, 2013). The drug approval system in Australia must keep pace with advances in science and research.

Research informing cancer treatment is constantly evolving. The development of effective novel therapies places greater pressure on the system to make such cancer treatment available to the target patient group. The advent of personalised medicines and increasing use of biomarkers in oncology to direct effective treatment and inform treatment options is an emerging and growing area in cancer research. It will mean a growing market of various medicines (Olver, 2013).

Specialised medications target molecular pathways within cancer cells and minimise the undesirable side-effects of traditional chemotherapies however, they are often more expensive and funding them within public health care systems poses significant challenges (Kaser 2010). Unlike traditional cytotoxic chemotherapy, which cannot distinguish between cancerous and non-cancerous cells, targeted therapies have less interference to non-cancerous cells.

Targeted therapy requires a companion diagnostic test to identify patients most likely to benefit from treatment. There are additional costs associated with the development of co-dependent technologies as well as an additional approval process. In vitro diagnostic medical devices (IVDs) used to identify biomarkers must also be registered on the ARTG as an approved medical device. An IVD determines the presence of a biomarker and must be registered as an approved medical device. IVDs are generally pathology tests and related instrumentation used to carry out testing on human samples, where the results are intended to assist in clinical diagnosis or in making decisions concerning clinical management (TGA, 2011). Therefore, the registration of a corresponding IVD is crucial to the effectiveness of the targeted treatment.

Intended patient groups are typically smaller because of better differentiation of disease subtypes and targeted nature of these medicines as treatment is contingent on the presence of a diagnostic biomarker. However, a larger cohort will undergo the diagnostic test to determine the presence of a biomarker, as not all people who use the IVD will present with a biomarker and go on to have the targeted treatment.

Cancer Council Australia/COSA summary recommendation:

Cancer Council Australia recommends that the Review Committee considers a coordinated approach to the TGA assessment of medicines for use in targeted cancer therapy and the co-dependent technology (IVD).

References:

Australian Government. 2014. Therapeutic Goods Act 1989, Act No. 21 of 1990 as amended in 2014, accessed on 18th December 2014 via <http://www.comlaw.gov.au/Details/C2014C00410>

Cheng AC, Nation RL. How can we improve access to new (and old) antibiotics in Australia? July 2013, MJA 199(2); 81-2

Chim L, Kelly PJ, Salkeld G, Stockler MR. Are cancer drugs less likely to be recommended for listing by the Pharmaceutical Benefits Advisory Committee in Australia? *Pharmacoeconomics*. 2010;28(6):463-75

Deloitte Access Economics. Access to cancer medicines in Australia. July 2013. Access via http://www.deloitte.com/assets/Dcom-Australia/Local%20Assets/Documents/Services/Corporate%20Finance/Access%20Economics/Deloitte_Access_to_cancer_medicines_in_Australia_July_2013.pdf

Kaser E, Shaw J, Marven M, Swinburne L, Boyle F. Communication about high-cost drugs in oncology-the patient view. *Ann Oncol*. 2010 Sep;21(9):1910-4

Mellor JD, Van Koeberden P, Yip SW, Thakerar A, Kirsa SW, Michael M. Access to anticancer drugs: many evidence-based treatments are off-label and unfunded by the Pharmaceutical Benefits Scheme. Internal Medicine Journal. 2012 Nov;42(11):1224-9

Olver I. 2011 .Improving cancer treatment by addressing legislative and regulatory issues Public Health. Dec; 125(12):876-81

Olver I. 2013. Challenges of accessing cancer medicines in Australia. Lancet Oncology. Oct 14(11):1040-2

Olver, I. 2014. Expedited access to cancer drugs. 6minutes. 23rd September 2014, access via <http://www.6minutes.com.au/blogs/6minutes-insight/cancer-drugs-expediting-the-review-process#comments>

Sansom L, Delaat W, Horvath J. 2014. Review of medicines and medical devices regulation: discussion paper, accessed via <http://www.health.gov.au/internet/main/publishing.nsf/Content/Expert-Review-of-Medicines-and-Medical-Devices-Regulation>

Therapeutic Goods Administration (TGA). 2011. Overview of the new regulatory framework for in vitro diagnostic medical devices (IVDs). Australian Department of Health.

Therapeutic Goods Administration. Prescription medicine registration process, version 2.0, May 2013. Australian Government Department of Health.

Therapeutic Goods Administration 'How the TGA regulates', last updated 28th October 2014, accessed on 18th December 2014 <https://www.tga.gov.au/how-tga-regulates>