Therapeutic Goods Administration Orphan Drugs Program: Discussion paper

Submission from the Clinical Oncology Society of Australia and Cancer Council Australia

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The **Clinical Oncology Society of Australia** (COSA) is the peak national body representing health professionals from all disciplines whose work involves the care of cancer patients.

Cancer Council Australia is Australia's peak national non-government cancer control organisation and advises the Australian Government and other bodies on evidence-based practices and policies to help prevent, detect and treat cancer.

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Proposed reform package – Cancer Council Australia/COSA recommendation

Orphan drug definition	(1) A medicine, vaccine or in vivo diagnostic agent is an orphan drug if it complies with this regulation. (2) It: (a) Must be intended to treat, prevent or diagnose a rare disease **AND** (b) Must not be commercially viable to supply to treat, prevent or diagnose another disease of condition.
Patient threshold	Increase and consider utility of in vivo diagnostic agents and vaccines separately
Charging model	Reduced fees – fee structure for new chemical entity, major variations and extension of indications

Summary of discussion paper:

The Therapeutic Goods Administration (TGA) Orphan Drugs Program was established through recognition that support was required to bring medicines which prevent, diagnose or treat small patient populations to market as low demand and the lack of financial incentive to develop or market these products restricted their availability to patients.

An amendment to the Therapeutic Goods Act 1989 was made in 1997 to include orphan drugs under section 16H.

Utilisation of the Orphan Drugs Program to date:

- 42% of all designations have been for antineoplastic drugs and immunomodulating agents
- 287 orphan drug designations have been made since 1998, 212 products went on to submit for registration of which 144 products were approved for market
- 1998/1999 to 2007/2008 there were an average of 14 designations per year. 2008/2009 to 2012/2013 there was an average of 27 designations per year
- 2012/2013 $5.9 million was foregone through waiver legislation, and in 2013/2014 $3.53 million was foregone

Orphan drugs are not limited to preventing, treating or diagnosing cancer, but any disease or condition which is likely to affect not more than 2,000 individuals in Australia at any time. An increase in submissions for orphan drug designation is observed to be largely the result of the evolution of 'new orphan' drugs. New orphan drugs are subdivisions of previously recognised common disease entities with therapies based on targetable mutations.

Addressing the components:

a. Orphan Drugs definition

Relevant legislation:

Therapeutic Goods Act 1989, Part 3B Section 16H Orphan Drug

> (3) A medicine, vaccine or in vivo diagnostic agent is an orphan drug if it complies with this regulation.
> (4) It:
>   (c) Must be intended to treat, prevent or diagnose a rare disease
>   or
>   (d) Must not be commercially viable to supply to treat, prevent or diagnose another disease of condition.

An orphan drug is defined by the TGA definition of a rare disease (as per *Therapeutic Goods Act 1989,* Part 1: Preliminary, Section 2 *'at any one point there are no more than 2,000 people with the disease in Australia[i]'*).

Who should be targeted with an orphan drugs programs?

Cancer Council Australia/COSA response:

The program aims to provide patients affected by a rare disease with access to a medicine to treat their condition, and provides access to a vaccine to treat, or in vivo diagnostic agent to support the diagnosis of a condition. This should continue.

The program provides an incentive for medicine developers to explore innovative therapeutics and technology for the benefit of this small group of patients that under normal market conditions may not attract interest. This should continue.

The definition of an orphan drug covers products used typically once (vaccine - to prevent, in vivo diagnostic - to diagnose) or multiple times (medicine - treatment), and products with broad reach (vaccine - prevent, in vivo diagnostic – to diagnose for treatment) or specific target (medicine - treatment). This seems appropriate.

The use and development of diagnostic tools and next generation sequencing have led to improved outcomes through screening and identification of relevant genetic abnormalities to advise treatment decisions. Improvements in disease classification have led to more reliable prognostic criteria and multidisciplinary management for patients of rare cancers.[ii] A greater understanding of cancer biology has enabled the development of targeted therapy with the ability to divide a cancer type into molecular subsets for more accurate study, discovery and development of targeted, effective treatments that are ineffective in other subgroups. For example: Axitinib is a selective tyrosine kinase inhibitor of vascular endothelial growth factor (VEGR) -1, VEGR-2 and VEGR-3. This treatment is effective in patients with advanced renal cell carcinoma, and indication for use after failure of one prior systemic therapy[iii]. The targeted nature of axitinib stops the growth of the tumour by blocking these proteins and cause fewer side effects than chemotherapy.

In recent years, the increase in targeted therapies has resulted in more specific indications cited on applications to the TGA to register a drug or the extension of existing indications. Based on this many new orphan drugs have received designation for specific indications consistent with the current TGA definition and regulations of the Orphan Drug Program, but are already well-established in the market as non-orphan drugs[iv]

Orphan drugs undergo the same assessment and evaluation by the TGA as non-orphan drugs prior to registration. Small patient groups are becoming more common as a result of the stratification of disease based on molecular characteristics. This impacts the ability of a researcher to apply a traditional study design such as a phase three trial that is usually sort to satisfy TGA assessment criteria. Obtaining significant patient numbers to prove efficacy and safety, and demonstrate significant improvement over standard treatments in a given population can be a barrier to early access to treatment. In addition, what is considered a 'significant outcome' can vary between the TGA and people affected by a rare cancer as there are limited options for effective treatment and survival rates once diagnosed are lower than more common cancers. Moving beyond overall survival as a primary outcome, a reasonable outcome from a study into a rare cancer would be addressing a clinically relevant advantage or a major contribution to patient care.

How can this be better reflected in the orphan drugs definition?

Cancer Council Australia/COSA response:

The orphan drugs definition should change to reflect the increase in well-established non-orphan drugs that qualify for orphan drug designation for specific indications. A small change

to the existing definition is suggested - the removal of 'or' which should be replaced by 'and' – see below.

Therapeutic Goods Act 1989, Part 3B Section 16H Orphan Drug

A medicine, vaccine or in vivo diagnostic agent is an orphan drug if it complies with this regulation.

> It:
>
> a. Must be intended to treat, prevent or diagnose a rare disease
>   **AND**
> b. Must not be commercially viable to supply to treat, prevent or diagnose another disease of condition.

This would ensure that a sponsor of a drug or an indication that target a small group of patients and is not commercially viable would qualify to receive the incentives that the Orphan Drugs Program provides.

Cancer Council Australia/ COSA Recommendations:

1. The Program should continue to target patients affected by rare diseases and be used in the prevention and diagnosis of rare diseases. The program should still target therapeutic product developers to explore medicines that affect this cohort of patients.

2. A greater understanding of cancer biology and targeted therapy has resulted in the increase in molecular subsets of 'common' cancers. As our understanding continues to grow so will the number of cancer subsets that form patient groups. These groups and their therapies are likely to result in the increase in 'rare cancers' as classified in the TGA Orphan Drugs Program because of the molecular uniqueness rather than tumour or organ classification of cancer. Well established non-orphan drugs which then can qualify for orphan designation for specific indications should only be given orphan drug status, and therefore receive the incentives of the program it:

   'Must be intended to treat, prevent or diagnose a rare disease
        AND
   Must not be commercially viable to supply to treat, prevent or diagnose another disease of condition.'

   Some drugs have the potential to be effective for various indications and across disease therefore increasing the market potential for purchase.

3. Further investigation into the potential impact of restricting definition to a specific indication or subset reach could determine if this restriction would be appropriate however, restricting the Program to disease stage would not be effective. This would not support access to treatment for people affected by rare diseases as these conditions are harder to diagnose, treatment options are limited, people affected usually present at a late stage and therefore, if the orphan drugs scheme was based on disease stage, many people may die before reaching a stage to access treatment.

Cancer Council Australia/COSA conclusion in bold:

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a. Restriction of disease stages for purpose of designation
b. Restriction on disease subsets/very specific indications for purpose of designation
c. A combination of A and B
d. Retain status quo

None of the above, our suggestion:

Therapeutic Goods Act 1989, Part 3B Section 16H Orphan Drug
A medicine, vaccine or in vivo diagnostic agent is an orphan drug if it complies with this regulation.
    It:
        Must be intended to treat, prevent or diagnose a rare disease
            AND
        Must not be commercially viable to supply to treat, prevent or diagnose another disease of condition.

Reason: point 2 of the recommendation.

b. Patient Threshold

Relevant legislation:

Therapeutic Goods Act 1989, Part 1: Preliminary, Section 2

A rare disease is a disease, or condition, likely to affect not more than 2,000 individuals in Australia at any time.

Is the current threshold appropriate for patient coverage?

Cancer Council Australia/COSA response:

The patient threshold has remained unchanged since the Program's inception in 1997.

Rare Voices Australia defines a 'rare disease' as any disorder or condition that is a life threatening or chronically deliberating disease that is statistically rare, with an estimated prevalence of 5 in 10, 000 people or, of similarly low prevalence and high level of complexity that special combined efforts are needed to address the disorder or condition. Based on the estimated Australian resident population at 30 June 2014 of 23, 490, 700, this would be a total of 11, 745 people[v]. There are more than 8,000 rare diseases, many of which are difficult to diagnose and collectively, rare diseases affect an estimated 6-8% of the Australian population[vi].

Rare Cancers Australia defines a 'rare cancer' as having an incidence of less than 6 per 100,000 Australian's per annum, and 'less common cancers' are those with an incidence of between 6 and 12 per 100,000 Australians per annum. Over 75% of deaths from rare or less common cancers occurring in Australians 50 years and over, and overall survival for rare and less common cancers as a group is largely unchanged since 1990[vii]

A rare disease, by TGA definition and therefore the threshold for orphan drug designation, is a condition that does not affect more than 2,000 individuals in Australia at any time[viii]. This currently reflects approximately 0.88 per 10, 000 people. Compared to other countries this is very low. The European Medicine Agency (EMA) patient threshold for orphan drug designation is not more than five per 10, 000 persons, and the US Food and Drug Administration is less than 200, 000 per year (6.37 per 10, 000). The EMA definition supports changes in population growth trend and is not a fixed number unlike Australia and the United States[ix].

Australian population growth and cancer:

When the Orphan Drugs Program was introduced in 1997 the Australian population was just above 18 and a half million people.[x] Since this time the population has increased to around 23.5 million[xi]

Incidence, all cancers, all persons[xii]:

- 1997 – 463.1/100,000 (81,019 new cases)
- 2011 – 484.1/100,000 (118,711 new cases)

Mortality, all cancers, all persons[xiii]:

- 1997 – 203.1/ 100,000 (35,109 deaths) 1 in 4 risk before 85 years
- 2011- 172.2/100,000 (43,147 deaths) 1 in 5 risk before 85 years

5 year relative survival, all cancers, all persons[xiv]:

- 1982-1987 46.9%
- 2006-2010 66.1%

These statistics demonstrate that more people are being diagnosed with cancer (all types) but are surviving longer. Although 5 year relative survival for all cancers combined has increased from 47% in the period 1982-87 to 66% in 2006-2010[xv], the same rate of increase in survival has not been even across all individual cancer types and especially not in rare cancers.

Early diagnosis is highly significant in improving patient survival and many Australians with rare or less common cancers had their outcomes compromised by late diagnosis.[xvi] The rate of increase is currently twice that of the population growth.[xvii]

Patient threshold for diagnostic technologies:

Therapeutic Goods Act 1989, Part 3B Section 16I (4) Orphan Drug

For designation as an orphan drugs: 'for a vaccine or in vivo diagnostic agent, the application must also state that the vaccine or agent will be administered in Australia to not more than 2,000 people in each year after it is registered for use for the disease or condition[xviii].'

'New orphan drugs' are increasingly common in oncology as a result of advancement in understanding the molecular biology of cancer and resulting in the identification of molecular subtypes. It has resulted in the treatment of cancer based on the presence of a specific biomarker. Targeted treatment has better outcomes as it targets patients most likely to respond and targets cancer cells while leaving healthy cells untouched, unlike traditional chemotherapy.

A co-dependent test provides a tool for clinical diagnosis and management to maximise effective intervention of a particular subset of cancer. Not all people who use the diagnostic agent to identify a biomarker will present with the biomarker and go on to have the corresponding treatment. The number of people using a vaccine or in vivo diagnostic agent will typically be greater than the patient group receiving treatment. This raises an issue of patient threshold for rare disease verses patient threshold for use of a vaccine or in vivo diagnostic agent to prevent or detect a rare disease. Crizotinib is indicated for the treatment of patients with anaplastic lymphoma kinase (ALK)-protein positive advanced non-small cell lung cancer (NSCLC). The identification of an overactive ALK enzyme requires ALK gene arrangement testing in NSCLC patients however, only about 1 in 20 patients will present as ALK-protein positive and go on to respond to crizotinib treatment[xix].

Cancer Council Australia/COSA Key messages and recommendations:

1. The patient threshold for the definition of rare disease should be reviewed as it has not changed in 20 years despite population growth and an increase in individual rare cancers. The current threshold lags behind international comparisons.

    Using prevalence (not more than 2,000 people affected at any time) depends on survival outcomes. Although rare cancers have not seen the same increase in survival as many common cancers, the research focus on the molecular biology of cancer will inform earlier diagnosis and target therapies in the future. Therefore using an incidence definition (like the US) or a number per 10, 000 population (like in the UK), would be a more accurate way of reflecting trends in population growth trends.

2. Vaccines and in vivo diagnostic agents will be used by more people than go on to use the corresponding drug for treatment. Therefore a patient threshold that is the same as the corresponding medicine threshold has potential to be restrictive. This should be considered when analysing patient threshold. To determine a threshold or applying orphan drug status for these products requires a greater understanding of how many people will utilise such therapies

Cancer Council Australia/COSA conclusion in bold:

   a. **Increase the patient threshold**
   b. **Retain the status quo**

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c. Charging Model

Relevant legislation:

Therapeutic Goods Act 1989, Division 2 – Fees and costs, Regulation 45

(12) The Secretary must waive the following fees:

   (a) a fee that would have been payable, but for this subregulation, for applying to the Secretary under subregulation 16I(1) to have a medicine designated as an orphan drug;
   (b) a fee that would have been payable, but for this subregulation, for the Secretary considering the application under regulation 16J;

(c) a fee that would have been payable, but for this subregulation, as part of the registration of a designated orphan drug.

Are changes needed to the charging model?

Cancer Council Australia/COSA response:

The TGA is funded by the industry on a cost recovery model. Therefore, any waiver of fees under the Orphan Drugs Program does not remove a cost, the cost of TGA resourcing for evaluation and assessment of applications is shifted to other (non-orphan) therapeutic applications to be covered. This increases the fees that non-orphan drug sponsors pay. This model is replicated when the PBAC reviews an application from a registered orphan drug for reimbursement. Industry could consider that the cost shift for covering orphan drug applications is not fair. The objective is to provide a sustainable system for people affected by rare diseases to access safe, effective treatment.

For the registration of a new chemical entity, this amounts to $221, 400 at the current (2014/2015) rate for application and evaluation fees. For a major variation or extension of indication, the fees waived are $85, 700 and $131, 600 respectively[xx]

The cost acknowledged above would not be considered prohibitive for sponsors but it should be acknowledged that removing this expense from sponsors, reduces the overall cost they seek to recoup through sales. It is difficult to determine the impact that introducing a fee scheme would have on the sponsors willingness to undertake research and development in therapeutic products for rare diseases.

Introducing a scheme that involves an initial fee waiver for new chemical entities and then regular fees for major variations and extension to indications could generate two responses. Sponsors may submit an application for a new chemical entity with more broad or multiple indications to avoid future fees, which would promote greater access to the product. Alternatively, it could generate an increase in the use of registered therapeutic products in an 'off label' capacity. 'Off label' use refers to use outside of the terms of registration by the TGA. Off-label use of medicines brings with it a number of clinical, safety and ethical issues.

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[xxi]. 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 has implications for affordability as the PBAC will only consider a medicine for reimbursement for the same indications as is registered on TGA. The system must encourage sponsors to register new discoveries and safe and effective uses for the medicine through the TGA.

A reduced fee structure for new chemical entities, major variations and extension of indications would introduce finances to the Orphan Drugs Program to cover some resource expenses, while still encouraging sponsors to development therapies for people affected by rare disease.

Cancer Council Australia/COSA Key messages and recommendations:
1. Do not want to encourage off label use or reliance on compassionate schemes which are unsustainable and unreliable. 2. Determine and introduce a reduced fee structure for the introduction of orphan drugs as new chemical entities, major variations and extensions of indications.
Cancer Council Australia/COSA conclusion in bold:
a. Initial fee waiver for designated orphan new chemical entities, but fee for variations **b. Reduced fees for designated orphan drugs** c. No fee waiver, with exceptions for applications under specific circumstances, e.g. paediatric access, specific demographics d. Retain the status quo

d. Is the TGA Orphan Drugs Program is still fulfilling its intended purpose?

(*Programs purpose: to provide an incentive to sponsors to bring medicines for a small population to market and in doing so make medicines available to patients that otherwise would not be available*)

Cancer Council Australia/COSA response:

Orphan drug legislation has successfully provided incentives for drug companies to bring products for rare diseases to market. It has stimulated research and development into therapies to treat rare cancers however, there is potential for increased outreach through change in patient threshold.

Orphan drugs are medicines used in the treatment, prevention or diagnosis of rare diseases /disease subtypes and/or are not commercially viable because of their small market potential. The Program provides an incentive for developers of pharmaceutical products to market therapies to the small patient population affected by rare diseases. Waiving the fees attributed to the evaluation and registration of a pharmaceutical product by the TGA results in an overall reduced expenditure of bringing the product to market and therefore the expenses a sponsor seeks to recoup through sales. Orphan drugs can apply to the PBAC for listing on the PBS and therefore their product is subsidised by the government, further reducing the cost to the patient.

To date, the Orphan Drugs Program has brought 144 products to market which may not have been available to patients of rare conditions through the standard channel of drug registration and reimbursement[xxii] (how many are cancer drugs?, provide an example)

The TGA Orphan Drugs Program still fulfils its intended purpose as an incentive scheme to support sponsors researching and developing medicines for a small patient group. It has supported the introduction of new medicines or extension of indications on existing non-orphan drugs available to patients of rare diseases.

Although not the topic of this discussion paper, reimbursement is crucial to the success of the TGA Orphan Drugs Program as generally, if there is no reimbursement the medicine will be too expensive and patients will not be able to afford or benefit from the orphan drug.

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