



Therapeutic Goods Administration Consultation: Orphan drug program

(2015 consultation outcomes and 2016 orphan drug program proposal)

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

November 2016

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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Introduction:

As stated in our response to the 2015 consultation paper¹, the Therapeutic Goods Administration (TGA) Orphan Drugs Program continues to fulfil its intended purpose as an incentive scheme to support the development of medicines targeted to a small population group and bringing these products to market. The program has supported the introduction of new medicines and the extension of indications to existing drugs, making these products available to patients of rare diseases who would not otherwise be able to access life prolonging or life improving medicines. Cancer Council Australia and the Clinical Oncology Society of Australia (COSA) support the continuation of this program and the proposed changes outlined in the 2016 consultation paper. In our view the changes reflect the advancements in the treatment of cancer influenced by our increased understanding of cancer biology.

¹ Cancer Council Australia and the Clinical Oncology Society of Australia. 2015. Joint response to Therapeutic Goods Administration Orphan Drugs Program consultation paper.

COSA and Cancer Council Australia responses to each of the specific aspects of the proposed TGA Orphan Drugs Program are below:

1. Rare disease threshold, seriousness of the condition:

- Threshold of 5/10,000 AND life threatening/chronically debilitating
OR
- Life threatening/seriously debilitating or serious and chronic condition AND that without incentives it is unlikely that marketing would generate sufficient return to justify the necessary investment

Q1. Do you support criterion one?

Cancer Council Australia and COSA agree with the proposed revision of the patient threshold.

We recognise the introduction of additional criteria to determine the seriousness of the condition for which the product will treat *in addition* to the patient threshold. This is important because the TGA would experience a substantial increase in the number of products qualifying for orphan designation if the assessment was based solely on a patient threshold. In turn, given the TGA works on a cost-recovery model, it would have implications for financial sustainability.

The revised patient threshold supports Cancer Council Australia and COSA's recommendation from the 2015 consultation. The current threshold of 2000 Australians lags behind international comparisons, does not account for population growth and no longer reflects how cancer types are classified and treated, and therefore the number of potential people within a particular treating cohort. Therefore our recommendation was for this threshold to be reviewed.

Products for which the condition exceeds the patient threshold but demonstrates that it targets a life-threatening or serious condition, can still seek orphan designation. However, the sponsor must also demonstrate that without the incentive of the fee waiver, the product is unlikely to provide a sufficient return to justify the necessary investment to bring it to market.

It is important to provide the additional option to sponsors of products that exceed the patient threshold. This criterion is particularly applicable for products with a wide population reach that prevent or diagnose a serious condition or may be used as a once off (such as vaccines or in vivo diagnostic agents). However, to achieve designation the sponsor must also demonstrate that the product will not be commercially viable. The TGA must provide more detail on the intended criteria to assess what is considered a 'sufficient return'.

2. Existing treatment and significant benefit over existing treatment:

- There is no existing therapy
OR
- If there is existing therapy, the product represents a significant benefit over existing therapies (clinically relevant advantage through improved efficacy, or improved safety)

or a major contribution to patient care is to be established based on comparison with the Australian standard model of care.

Q2. Do you support criteria two?

Cancer Council Australia and COSA support the introduction of advantageous treatment for rare diseases. The addition of criterion two recognises the importance of bringing products to market that fulfil an unmet need or provide significant clinical benefit in line with Australian standard models of care. It is important to provide access to products that are supported by best practice care delivered in Australia.

As reported in our submission to the 2015 consultation², results of an audit of chemotherapy protocols and the use of off-label products in evidence-based guidelines within a specialist cancer centre in Australia found that 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 combination³. It found that over 90% of 'off label' products were supported by evidence-based treatment guidelines or phase two or three clinical trials data. This demonstrates a significant gap between best practice care and access to registered products (which in turn impacts on affordability). This highlights the importance of considering the Australian context and why we support criterion two.

3. Orphan condition, medical plausibility and biomarkers:

- A justification of medical plausibility is required to support the orphan indication and to support subgrouping of indications

Q3. Do you support criteria three & four?

The evidence of a therapeutic product's safety, quality, and efficacy for a particular indication are critical components of a regulator's review of a product prior to use by the intended market. Therefore, Cancer Council Australia and COSA support the introduction of criteria three and four.

In our response to the 2015 consultation⁴, we acknowledged that 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 options. The personalised method of treatment of some cancer types increases the probability of the treatment's effectiveness in people with a particular indicator, such as a specific genetic mutation, and the probability of it being ineffective in other subgroups. However, although the presence of a particular predictor increases the probability of a positive response, this may not be the case for all patients. People with the disease but not the predictive mutation could possibly benefit from use of the product when other options are exhausted. Alternatively, an individual with the predictive mutation may not respond positively as

² Cancer Council Australia and the Clinical Oncology Society of Australia. 2015. Joint response to Therapeutic Goods Administration Orphan Drugs Program consultation paper.

³ Mellor JD, Van Koeberden P, Yip SWK, Thakerar A, Kirsas SW and Michael M 2012. Access to anticancer drugs: many evidence-based treatments are off-label and unfunded by the Pharmaceutical Benefits Scheme. Internal Medicine Journal, vol. 42 (11), pp. 1224-29.

⁴ Cancer Council Australia and the Clinical Oncology Society of Australia. 2015. Joint response to Therapeutic Goods Administration Orphan Drugs Program consultation paper.

expected. Therefore we should not exclude the possibility of its reach especially at the early phase of testing - although there could be the risk of complications when we are uncertain that the treatment will be effective for an individual outside of the predictive population.

Q4. Do you support the proposed consideration of paediatric indications?

Cancer Council Australia and COSA did not directly address this specific aspect of the program during the 2015 consultation but see its application similar to the subgroup criteria three and four. Therefore, if a product's effectiveness can be proven in a paediatric population and not effective in an adult sub group then the product could qualify for orphan designation. However, clinical trial methodology may need to be modified to demonstrate this comparison.

4. Modifications to the designation process:

Q5. Do you support the proposed changes to the designation process and timing of automatic lapsing?

Cancer Council Australia and COSA did not specifically raise this point during the 2015 consultation. However, we support the proposed introduction of a lapse designation after a particular time period (noted as potentially 3 - 6 months) or cancellation by the TGA if new evidence emerges that no longer supports the designation.

We agree that the change ensures that data provided within the application is accurate. We did consider whether this would impact on the ability to bring products to market earlier or in a timely way however, recognise that approved orphan designations are eligible to apply for listing through the early access and priority TGA schemes that have recently been proposed from the Medicines and Medical Devices Review⁵. In addition, the 2016 Orphan Drugs Program discussion paper reported that between the period of 2011-2015, 30% of orphan designation applications were lodged within three months of designation, and 57% within a year, and 34% had not lodged a registration application within a five-year period⁶. Therefore, suggesting that the majority of applications for registration would be submitted prior to their designation lapsing, or could be encouraged to apply sooner.

- Continuation of a complete fee waiver for all applications:

In our submission to the 2015 consultation, Cancer Council Australia and COSA recommended a reduced fee structure for designated orphan drugs depending on whether the application was for new chemical entities, major variations or extension of indications to existing Australian Register of Therapeutic Goods (ARTG) listings. The rationale was to support the financial sustainability of the program, but we were conscious that introducing a fee structure could be prohibitive and continue to encourage off label use or reliance on compassionate schemes. The rationale also took into account the situation where the sponsor of an existing listing could apply for orphan designation on an extension to that

⁵ Therapeutic Goods Administration. 2016. Consultation: Expedited pathways for prescription medicines. Eligibility criteria and designation process. Version 1.0, October 2016. Department of Health, Australian Government.

⁶ Therapeutic Goods Administration. 2016. Consultation: Orphan drug program. 2015 consultation outcomes and 2016 orphan drug program proposal. Version 1.0, October 2016. Department of Health, Australian Government.

indication although the product itself, given it's listing for multiple indications, may be financial viable.

The consultation paper reports that 75% of the rejected TGA orphan designation applications (2011-2015) went on to lodge a non-orphan registration application for the same indication⁷. This could indicate that it is unlikely that the absence of TGA orphan status would prevent product development for most of these products. Although the majority of rejected applications went on to lodge a non-orphan registration application, 25% did not and this could prohibit patients receiving treatment where there is no alternative, or receiving a therapy that has significant benefit over the products they can access. More needs to be known about the 25% of applications that did not go on to lodge a non-orphan registration application.

- Can seek external advice in relation to the criteria

Like other regulatory processes, the TGA Orphan Drugs Program must be able to refer an application or component of the application for expert advice, and given the TGA has structures in place for these requests could draw on existing expert review panels.

5. Other considerations:

Q6. Are there any other key issues that should be considered in developing the changes to the orphan drugs program?

- As noted earlier, if the product already exists on the market for another indication, whether it is an orphan designation or not, it means the product has multiple applications in clinical practice making it's collective market larger. It is unclear whether the assessment of financial viability will include all indications for that product or just for the individual orphan indication. This could encourage sponsors applying for multiple orphan designations and receive a complete fee waiver for each application, even when the product is commercially viable.
- The additional criteria must be assessed consistently. Guidance on the assessment of criteria including the demonstration of 'significant benefit', 'serious or chronic conditions', and evidence to support that bringing a product to market is 'unlikely to generate sufficient return', would support transparency in decision making.
- Although not the topic of this consultation, the registration of therapeutic products is a critical step to patient access and also for the application of reimbursement to the Pharmaceutical Benefits Advisory Committee. In many situations the price of a product not listed on the Pharmaceutical Benefits Scheme can make access prohibitive to many people. To better support the program, other department and regulatory review processes need to be coordinated and where possible, conducted in parallel to aid earlier access to approved products. The Department of Health is investigating the implementation of Medicines and Medical Devices review

⁷ Therapeutic Goods Administration. 2016. Consultation: Orphan drug program. 2015 consultation outcomes and 2016 orphan drug program proposal. Version 1.0, October 2016. Department of Health, Australian Government.

recommendations including an expedited review process which applies to orphan and non-orphan drug designations.

Conclusion:

The proposed changes to the TGA Orphan Drugs Program support the introduction of products to market for conditions with no existing treatment, or that represent a significant benefit over existing treatment while ensuring medical plausibility for subsets. On this basis, Cancer Council Australia and COSA are broadly supportive of the reforms, noting the need for more information to make a more informed assessment of benefit versus risk.