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Therapeutic Goods Administration

Orphan drugs program

Discussion paper

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Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <<http://www.tga.gov.au>>.

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Contents

Background	4
The objective of the orphan drugs program	4
Incentives	5
Utilisation of the program	6
Objective of this review	7
Current situation	7
Contemporary context - what is a rare disease?	7
Examples of orphan drugs	9
The new orphan drug paradigm	11
International equivalents	13
The European Medicine Agency (EMA) orphan drugs program	13
US Food and Drug Administration (FDA) orphan drugs program	14
Possible reform options	16
Orphan drug definition	16
A. Disease stages	16
B. Limiting indications and disease subsets	17
C. A combination of A and B	18
D. Retain the status quo	18
Patient threshold	19
A. Consider a new threshold	19
B. Retain the status quo	19
Charging model	19
A. Initial registration free, fees payable for all subsequent changes	21
B. Reduced fees for designated orphan drugs	22
C. Abolish the fee waiver for orphan drugs	22
D. Retain the status quo	22
Possible reform packages	23
Option one	23
Option two	23
Option three	24
Option four	24

Background

The objective of the orphan drugs program

In a broad sense the orphan drugs program can be considered a type of joint community service or public health obligation of the Government and prescriptions medicine industry. The original intention, as set out in the Explanatory Memorandum at the time of the amendment to the Therapeutic Goods Regulations in 1997, states that:

"The Regulations...Provide for an orphan drugs program by waiving fees in relation to the designation, evaluation and registration of orphan drugs, Orphan drugs are drugs used in the treatment, prevention or diagnosis of rare diseases, and are often not commercially viable because of their small market potential. The amendments provide an opportunity for sponsors to market orphan drugs in Australia at a reduced cost through the waiving of application and evaluation fees..."

When the program was established, it was intended 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.

Interestingly, the Explanatory Memorandum defines an orphan drug as one that is used in the treatment, prevention or diagnosis of rare disease, **and** is not, generally, commercially viable. However, this second aspect is **not reflected as a requirement** in the definition of an orphan drug as set out in regulation 16H, which states an orphan drug is (a) intended to treat, prevent or diagnose a rare disease; **or** (b) must not be commercially viable to supply to treat, prevent or diagnose another disease or condition.

The current definition of an orphan drug is set out in section 16H of the Regulations (below) and remains unchanged since the program commenced.

16H Orphan drug

(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;

or

(b) must not be commercially viable to supply to treat, prevent or diagnose another disease or condition.

(3) It is not an orphan drug if any of the following persons or bodies has refused to approve it for use for the disease for a reason related to the medicine's safety:

(a) the Secretary;

(b) the Food and Drug Administration of the United States of America;

(c) the Medicines Control Agency of the United Kingdom;

(d) the Bureau of Pharmaceutical Assessment of Canada;

(e) the Medical Products Agency of Sweden;

(f) the Medicines Evaluation Board of the Netherlands;

(g) the European Agency for the Evaluation of Medicinal Products.

(4) It is not an orphan drug if it has been registered for use for the disease or condition before 1 January 1998.

(5) However, it may be registered before 1 January 1998 for another use or indication.

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

Regulation 16 I(4) concerning applications for designation as an orphan drug, requires: “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.”

Incentives

When the Orphan drugs program was established it was generally recognised that support was required to bring these products to market due to low demand and the lack of financial incentive to develop or market a medicine for such a small patient population. At the time, this support was in the form of waiving fees for evaluation and registration, this was the minimum support given by other regulators with orphan drugs programs. Some jurisdictions have extended this support, providing tax benefits, increased periods of market exclusivity and grant programs for the development of drugs for rare diseases.

In Australia, Regulation 45(12) provides a waiver of fees associated with an application for designation, for fees considering the application and for fees as part of the registration of a designated orphan drug.

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.

For a new chemical entity, this amounts to \$221,400 at the current (2014/15) rate for application and evaluation fees. For a major variation or extension of indication, the fees waived are \$85,700 and \$131,600 respectively. Because TGA is fully industry cost-recovered, any waiver of fees by TGA for orphan drugs in effect shifts the cost of the work done by TGA in orphan drug evaluation to sponsors of other products, even though they may not have orphan drugs within their product portfolio.

Beyond the TGA, orphan drug designation also results in a waiver of fees for applications to the Pharmaceutical Benefits Advisory Committee for consideration of Pharmaceutical Benefits Scheme funding. The impact of the current arrangements on the PBS Cost Recovery

arrangements was noted in an independent review in 2011¹ with the following recommendation being made: “The Committee recommends that the Minister consider the inclusion of total government expenditure and total projected profit as factors to be considered in deciding whether an application should be granted a fee exemption or waiver, even where those applications may involve small patient numbers”.

Utilisation of the program

The key findings of an internal review of the program in late 2013 are:

- 287 orphan drug designations have been made since 1998.
- Between 1998/99 and 2007/08 there was an average of 14 designations per year.
- From 2008/09 to 2012/13 there was an average of 27 designations per year.
- Almost half of all designations, 48%, were for drugs for neoplastic disorders and haematological disorders.
- 42 % of all designations were for antineoplastic drugs (cancer therapy) and immunomodulating agents.
- Of the 287 designations, 74 % (212 products) have been followed by a submission for registration. Of these 68 % (144 products) have been approved.
- Approximately \$35 million of potential evaluation fees have been foregone since commencement of the program. In 2012/13 \$5.9 million was foregone while in 2013/14 \$3.53 was foregone.

The key finding arising from this internal review was the increasing number of orphan drug designations and submissions each year since program inception. The amount of foregone evaluation revenue in 2012/13 (\$5.9 million) and 2013/14 (\$ 3.53 million), equivalent to approximately 5% of total income from evaluation, was the highest annual cost for the program to date, and based on current projections and industry knowledge is expected to stay at this higher level and potentially increase.

The increase in submissions for orphan drug designation is observed to be largely the result of the evolution of “new” orphan drugs, as discussed in Section 3.

When proposing options for reform of the orphan drug program, the cost of delivering the program and the mechanisms for ensuring that cost is covered also needs to be considered.

¹ Independent Review of the Impact of Pharmaceutical Benefits Scheme (PBS) Cost Recovery, November 2011 <<http://pbs.gov.au/publication/factsheets/independent-review-PBS-cost-recovery.pdf>>

Objective of this review

With the focus of pharmaceutical companies increasingly turning towards orphan drugs² it is timely to consider if the orphan drug scheme for market authorisation as currently in place has a tangible impact on supporting medicine availability to the intended patient population.

The financial impact of the current program needs to also be considered in light of the amount of revenue currently foregone by the TGA and the flow on effect to the Pharmaceutical Benefits Scheme, especially given the expected increase in the number of orphan drug applications.

The Australian program is currently intended to help make medicines available to sufferers of rare diseases, that is, diseases or conditions likely to affect not more than 2000 individuals in Australia at any one time.

As the Orphan Drugs Program approaches 20 years in operation it is fitting to consider if the program is still fulfilling its intended purpose; if changes are required to ensure the program objectives are continuing to be met; and that the program remains viable as pharmaceutical drug development moves towards more targeted treatments.

Current situation

Contemporary context - what is a rare disease?

A **rare disease** is defined in Regulation 2 of the *Therapeutic Goods Regulations 1990* as “a disease, or condition, likely to affect not more than 2,000 individuals in Australia at any time. While an **orphan drug** must be intended to “treat, prevent or diagnose a rare disease”.

At the time the orphan drugs program was established, the Australian population was approaching 20 million and 2000 was chosen as the patient threshold on the basis of it representing an incidence of 1 in 10,000. Since that time, the population has increased to around 23.5 million and the patient threshold has remained the same, so the required incidence would have decreased slightly.

Rare Voices Australia, the peak body representing Australians with rare diseases, define a rare disease as any disorder or condition that is life-threatening or chronically debilitating disease which is statistically rare, with an estimated prevalence of 5 in 10,000 or of similarly low prevalence and high level of complexity that special combined efforts are needed to address the disorder or condition.

As more effective treatment options have led to increased life expectancy some of the diseases classified as rare are exceeding the patient threshold for a rare disease according to the current definition. Yet within the community the disease is still considered to be a rare disease. An example of this is haemophilia A, Table 1, below, illustrates how the number of sufferers has increased over time, as a result of better treatment, and how the disease no longer meets the TGA definition of a rare disease.

² Rockoff J, Drug makers see profit potential in rare diseases, Wall Street Journal, Jan 2013.

Table 1: Increasing prevalence over time of a disease which in this case has better treatment and hence survival leading to higher prevalence.

Number in ABDR Registry*				
HMA	2009-10	2010-11	2011-12	2012-13
Factor VIII Deficiency (Haemophilia A)	1,793	1,852	1,918	1,954
Asymptomatic Carrier Factor VIII Deficiency (Haemophilia A)	210	233	253	259
Symptomatic Carrier Factor VIII Deficiency (Haemophilia A)	82	95	103	117
Acquired Factor VIII Inhibitor (Acquired Haemophilia A)	33	40	47	61

*Figures from the Australian Bleeding Disorders Registry (ABDR) Annual Report 2012-13 published by the National Blood Authority

Given the factors above – increasing population and better patient care – to ensure patient access to medicines is not inadvertently affected, consideration could be given to update the patient threshold from a static figure to use a measure of prevalence or a percentage of the population. For comparison, Table 2 summarises the patient threshold used by other regulators with orphan drugs programs. It can be seen that the current Australian patient threshold for orphan drug definition is much more restrictive in terms of patient prevalence than these other major regulators.

Table 2: Comparison of patient thresholds for orphan drug designation used by comparable regulators.

Regulator	Patient Threshold
TGA	Not more than 2000 at any time (currently 0.88 in 10,000)
US Food and Drug Administration	Fewer than 200,000 per year (6.37 in 10,000)
European Medicines Agency	5 in 10,000
Health Canada	5 in 10,000
SwissMedic	5 in 10,000
Singapore HSA	Less than 20,000 (37.7 in 10,000)

Examples of orphan drugs

Table 3 provides examples of medicines that were designated and registered as orphan drugs around the time program commenced.

Table 3: Examples of orphan drugs designated in 1999-2001 (soon after program commencement)

Drug ³	Sponsor	Date of designation	Date of registration in Australia	Indication
Anagrelide hydrochloride (Agrylin)	Orphan Australia	16.10.1998	23.11.1999	For the treatment of essential thrombocytaemia
Factor VIII [rDNA]; (KOGENATE FS, SF; HELIXATE FS, SF)	Bayer	17.6.1999	28.2.2001	For the treatment and prophylaxis of bleeding in haemophilia A (congenital factor VIII deficiency) in previously treated and untreated patients, and in patients with Factor VIII inhibitors (neutralising antibodies) who continue to respond to Kogenate FS (ie in whom haemostasis is achieved) [Kogenate FS does not contain von Willebrand's Factor and hence is not indicated in von Willebrand's disease].
Fomivirsen sodium (VITRAVENE)	Ciba Vision Australia Pty Ltd	1.4.1999	2.5.2000	For the local treatment of cytomegalovirus (CMV) retinitis in patients with acquired immunodeficiency (AIDS).
Icodextrin 7.5% (EXTRANEAL PERITONEAL DIALYSIS SOLUTION)	Baxter Healthcare Pty Ltd	16.10.1998	16.12.1999	For the treatment of life threatening, End Stage Renal Disease, for those patients who have been identified as requiring the specialised treatment of peritoneal dialysis, and who have subsequently demonstrated significantly reduced ultrafiltration with intraperitoneal hyperosmolar glucose.
Imiglucerase (CEREZYME)	Genzyme Australia	16.10.1998	17.5.1999	For enzyme replacement for patients with a confirmed diagnosis of Gaucher's disease.

With the exception of Icodextrin, early orphan drugs were generally for broad indications related to a rare 'whole' disease. Icodextrin is for a specified stage of a much broader disease and for a very narrow indication within that disease stage. From the table of orphan drugs published on the TGA website (<http://www.tga.gov.au/orphan-drugs>), while this was unusual for early orphan drugs, there are several other examples where such indications were relied upon for early orphan drug designation. It was more common to rely on broader indications and "whole" diseases when the program commenced.

³ Data extracted from the Designated Orphan Drugs table on the TGA website <<http://www.tga.gov.au/orphan-drugs>>, examples were selected where the date of designation and registration was included.

For comparison, Table 4 provides examples of medicines that have been designated as orphan drugs more recently.

Table 4: Examples of medicines more recently designated as orphan drugs

Drug ⁴	Sponsor	Date of designation	Date of registration in Australia	Indication
Adalimumab (HUMIRA)	AbbVie Pty Ltd	02/11/2012	24/6/2014	For the treatment of active Crohn's Disease defined as a Paediatric Crohn's Disease Activity Index (PCDAI) score >30 in paediatric patients (6-17 years of age) who have had an inadequate response to conventional therapy, or who are intolerant to or have contraindications for such therapies.
Bevacizumab (AVASTIN)	Roche Products Pty Ltd	21/03/2014	Yet to be registered for this indication	For the treatment of persistent, recurrent Stage IV carcinoma of the cervix.
Drisapersen	Baxter Healthcare Pty Ltd	10/12/2013	Yet to be registered for this indication	For the treatment of patients with Duchenne muscular dystrophy (DMD) bearing certain mutations that are amenable to treatment with exon 51 skipping.
Ramucirumab (Cyramza)	Eli Lilly Australia Pty Limited	17/09/2013	Yet to be registered for this indication	The indication is for the treatment of patients with advanced gastric cancer or gastro-oesophageal junction adenocarcinoma after prior chemotherapy.

The above examples illustrate the nature of applications for designation that are commonly received now. Generally the indications are very narrow either through being for a molecularly defined subset of a disease or limited to very specific stages of a disease. Although not a new phenomenon, it is now usual practice for orphan drug indications to be this specific. This specificity may be the result of targeted treatments or reflect the way these drugs are developed. Many oncology drugs are initially tested in those with metastatic disease (i.e. the worst stage of the disease where there are no other options), which is only a subset of those diagnosed with that cancer.

⁴ Data extracted from the Designated Orphan Drugs table on the TGA website <<http://www.tga.gov.au/orphan-drugs>>, examples were selected where the date of designation and registration was included.

The new orphan drug paradigm

Since the inception of the Orphan Drug Program there have been developments in the definition and recognition of 'rare diseases'. These have included improvements in technology to diagnose and identify rare diseases and subtypes of diseases, and in the ability to tailor therapies for these diseases and disease subtypes. Rare Voices Australia, the peak body representing Australians with rare diseases, claims there are between 6,000 and 8,000 known rare diseases. It is estimated that a rare disease will affect 1 in 12 people, or 8 per cent of the Australian population. Concomitantly there has been a significant increase in the number of applications for orphan drug designation and applications for market authorisation for such drugs.

Much of the increase in applications for designation is due to what can be classified as "new orphans"⁵. These are subdivisions of previously recognised common disease entities, such as breast cancer and lung cancer, with therapies based on targetable mutations. These "new orphans" are mostly for oncology and haemato-oncology indications. For major innovator pharmaceutical companies this era of new medicine development appears to be a significant part of their business model. Highly specialised medicines for smaller population groups are resulting in high cost treatment regimens funded by patients and/or public schemes. This situation is not unique to Australia. Approximately 33%, 9 of 27 new medicines, approved in the US in 2013 were for orphan drugs^{6,7}. The European Medicines Agency (EMA) reports similar growth with regard to orphan drug designation in Europe⁸.

Many of the "new orphans" have received orphan drug designation for specific indications, consistent with the current TGA definition and Regulations, but are already well-established in the market for non-orphan drug indications. For these medicines it is difficult to differentiate the relative contribution of the orphan drug sales, however, from data derived from www.pbs.gov.au and https://www.medicareaustralia.gov.au/statistics/pbs_item.shtml, for a selection of drugs illustrates that many are associated with significant annual sales, as shown in Table 5.

⁵ Reardon, S (2014) Regulators adopt more orphan drugs, *Nature*, 508:16-17.

⁶ US FDA Novel New Drugs 2013 Summary, <<http://www.fda.gov/downloads/drugs/developmentapprovalprocess/druginnovation/ucm381803.pdf>> accessed 7.8.14

⁷ Phillips, M.I. (2013) Big Pharma's new model in orphan drugs and rare diseases, *Expert Opinion on Orphan Drugs*, 1(1).

⁸ Taylor, L (February 2013) EMA expecting 150+ orphan drug designations in 2013, *PharmaTimes Online* <<http://www.pharmatimes.com/article/13-02-19/EMA-expecting-150-orphan-drug-designations-in-2013.aspx>> accessed 16.7.13.

Table 5: Australian PBS Sales Estimates for a selection of drugs with orphan and non-orphan indications for the 2013/2014 financial year

Drug	Australian PBS Sales Estimate ⁹
Infliximab	\$6,389,239
Adalimumab	\$84,571,756
Rituximab	\$53,418,758
Bevacizumab	\$41,010,892
Abraxane (paclitaxel nanoparticle albumin bound)	\$15,481,174
Denosumab	\$28,533,491
Zoledronic acid	\$5,573,028

In addition, many of the “new” orphan drugs that are only registered for orphan indications are associated with significant annual sales, despite their small target populations based on data derived from data www.pbs.gov.au and https://www.medicareaustralia.gov.au/statistics/pbs_item.shtml for a selection of medicines, as illustrated in Table 6 below.

Table 6: Estimated Australian PBS Sales for selected drugs that are only registered for orphan indications for the 2013/2014 financial year

Drug	Australian PBS Sales Estimate ¹⁰
Imatinib	\$25,574,354
Bortezomib for myeloma, mantel cell lymphoma ¹¹	\$16,636,803
Lenolidamide for myeloma	\$19,260,462
Dabrafenib	\$3,481,790

⁹ Australian sales estimates were calculated from the number of services for each PBS item number for the drug in question as recorded on Medicare Statistics, multiplied by the Dispensed Price for Maximum Quantity (DPMQ). The DPMQ multiplied by services for all item numbers for the drug were totalled and then divided by 3 to give an estimate of revenue returned to sponsors.

¹⁰ Australian sales estimates were calculated from the number of services for each PBS item number for the drug in question as recorded on Medicare Statistics, multiplied by the DPMQ. The DPMQ multiplied by services for all item numbers for the drug were totalled and then divided by 3 to give an estimate of revenue returned to sponsors.

¹¹ The PBS sales for this product do not correspond exclusively to the orphan indications.

While the priority of ensuring availability of treatments for rare diseases remains, it is timely to consider if the Orphan Drugs Program in its current form, with the shifting market focus, is achieving this in the most effective way possible.

International equivalents

The European Medicine Agency (EMA) orphan drugs program

The criteria for orphan drug designation by the EMA are:

1. A medicinal product shall be designated as an orphan medicinal product if its sponsor can establish:

(a) that it is intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand persons in the Community when the application is made, or that it is intended for the diagnosis, prevention or treatment of a life-threatening, seriously debilitating or serious and chronic condition in the Community and that without incentives it is unlikely that the marketing of the medicinal product in the Community would generate sufficient return to justify the necessary investment;

and

(b) that there exists no satisfactory method of diagnosis, prevention or treatment of the condition in question that has been authorised in the Community or, if such method exists, that the medicinal product will be of significant benefit to those affected by that condition.

In addition, decisions relating to orphan drug designation are referred to the Committee for Orphan Medicinal Products (COMP), whose responsibilities include: providing opinions on designation; advising the Commission on establishment and development of a policy on orphan medicinal products; assisting the Commission on international liaison; assisting the Commission in drawing guidelines; contributing to Protocol Assistance (especially significant benefit).

The key designation criteria considered by the EMA and the COMP are:

1. Rarity (prevalence) of the condition or the return of investment
 - where it is a medical condition affecting not more than 5 in 10,000 in the European Community (around 250,000 people); or
 - without incentives it is unlikely the marketing of the product would generate sufficient return to justify the necessary investment.
2. Seriousness
 - Is the condition life-threatening or chronically debilitating?
3. Alternative methods authorised
 - If a satisfactory treatment method exists the sponsor should establish that the product will be of significant benefit.

At a recent Worldwide Orphan Medicinal Designation Workshop (March, 2014), it was noted that the return of investment is rarely, if ever relied on by sponsors for justification of orphan medicine status.

The inclusion of the “significant benefit” criterion, while allowing for discretion in decision making (see below), is the subject of ongoing discussion and debate in the EU. There is considerable subjectivity around the meaning of significant benefit and how to determine if a method, prevention or treatment is satisfactory. The paper “Significant benefit of orphan drugs: concepts and future developments”¹² outlines some of the issues with this criterion.

Although controversial, the inclusion of significant benefit as well as referral to the COMP allows for some discretion in decision making regarding orphan drug designation for specific indications. While not enshrined in the current definition, the EMA generally tries to avoid designation for disease subsets unless it can be shown that the drug cannot be used in any other stage or subset of the primary disease, for example the drug might target specific biomarkers or bind to a particular surface antigen. However through the subjectivity of the alternative method/significant benefit criteria and the COMP, there is scope for designation on the basis of these features.

US Food and Drug Administration (FDA) orphan drugs program

The FDA defines an orphan drug as a “drug or biological product intended for use in a rare disease or condition”, where a rare disease or condition is one that affects <200,000 people in the USA.

If designated, the sponsor may be eligible for the following financial incentives in relation to the product:

- Tax credits – 50% of clinical trials costs
- Waiver of marketing application user fee – over \$2million
- 7-year marketing exclusivity if first approved

The FDA process for determining orphan drug designation involves:

1. Determining the disease/condition that would be treated, diagnosed or prevented by the drug or biologic
 2. Determining if it is a rare disease
 - For treatments prevalence must be less than 200,000 people
 - For diagnostics, need to consider all who would be subjected to diagnosis per year
 - For prevention, everyone who is at risk of the disease is counted per year.
- a. If the disease/condition is common (ie occurs in >200,000) can grant orphan designation for use in an orphan subset. However this does not apply to “salami slicing” orphan subsets. For example:
 - A drug proposed to be used to treat breast cancer patients refractory to first-line treatment, unless there is some property of the drug that would restrict use, this subset **would not be permitted**.

¹² EMA, Significant benefit of orphan drugs: concepts and future developments, January 2012, EMA/326061/2012.

- A drug that will act against a surface antigen found only in a rare subset of breast cancer cases and would not act in breast cancer cases without the surface antigen **would be permitted.**
- A drug that targets a specific genetic mutation found only in a small subset of colon cancers **would be permitted.**

3. Is the scientific rationale sufficient?

- Evidence must be provided showing the drug holds promise for being effective in treating/preventing/diagnosing disease.

Similar to the EMA process, there is some discretion in decision making regarding orphan drug designation for disease subsets under certain circumstances.

The FDA also has access to the EU COMP consideration of orphan drugs as well for additional advice for orphan drug designation.

Possible reform options

While the original policy intent of the scheme remains there are 3 areas of consideration for possible reform: orphan drug definition, patient threshold and possible charging models. Each of these areas has multiple options for consideration. From these options, several combinations for reform could be selected to address the objectives of this review. Table 7 below summarises these options, which are discussed in more detail in the following sections.

Table 7: Possible options for each of the areas of consideration

Orphan drug definition		Patient Threshold	Charging Model
Question	Who should be targeted with an orphan drugs program? How can this be better reflected in the orphan drugs definition?	Is the current threshold appropriate for patient coverage?	Are changes needed to the charging model?
Options	A. Restriction of disease stages for purpose of designation	A. Increase the patient threshold	A. Initial fee waiver for designated orphan NCEs, but fees for variations
	B. Restrictions on disease subsets/very specific indications for purpose of designation	B. Retain the status quo	B. Reduced fees for designated orphan drugs
	C. A combination of A and B		C. No fee waiver, with exceptions for applications under specific circumstances, e.g. paediatric access, specific demographics
	D. Retain the status quo		D. Retain the status quo

Orphan drug definition

In response to the increasing number of ‘new’ orphan drug applications being received, it is worthwhile considering if the current definition is adequately addressing the original policy objective (to provide an incentive to sponsors to bring medicines for a small population to market) and in doing so making medicines available to patients that otherwise would not be available.

Any changes to the current definition would require amendment to the Regulations.

A. Disease stages

As treatments are becoming more targeted, a number of applications for orphan drug designation have been on the basis of a specific disease stage.

Of the 72 orphan drug designations from 2011-2013, 18 were on the basis of the stage of the disease being treated.

One of the key issues associated with using a disease stage, for example “last line” in cancer treatment, as the basis for an orphan designation, is that whilst it may satisfy the definition of a rare disease for patients at a specific point in time, ultimately most, if not all, sufferers of that particular cancer will reach the ‘rare disease’ stage. The use of pomalidomide for “last line” treatment of myeloma is an example of this.

The disease myeloma is an example of an incurable cancer that has seen an increase in incidence as a result of effective treatments, resulting in survival times almost doubling in the last 20 years. The current prevalence in Australia is around 6,000, well above the current orphan designation threshold for the whole disease. Orphan drug status has been designated for pomalidomide for “last line” treatment of myeloma, as not all with this disease are at the “last line” stage, yet. However, given the incurability of this disease, this “last line” treatment will eventually capture most, if not all, of those with myeloma at some point.

This example raises the question of whether allowing “last line” treatment to define a rare disease is in the spirit of the orphan drugs program.

Currently the specification of the stage of the disease is regarded as the “disease” for the purpose of Regulation 16H(2)(a). Limiting disease to mean all stages of the disease, not a specific stage would require an amendment to this regulation to provide greater clarity of the definition.

However, with the shifting development of medicines to more targeted treatments, continued consideration of the disease stage as the disease could be a better approach.

B. Limiting indications and disease subsets

Under the current definition, TGA has been presented with four different types of medicines seeking orphan drug designation.

1. “Classic” orphan drug - will be used for extended or on-going treatment for a rare disease (i.e. a disease that overall is of very very low prevalence, even when all stages are included) with a prevalence in Australia of fewer than 2000 persons;
2. Vaccines and in vivo diagnostic agents;
3. Treatments that are used once only (single administration or for a single brief period); and
4. Products to treat diseases or sub-classifications of diseases defined by one or more specific mutations.

It is the fourth category that captures the ‘new’ orphan drugs, in particular treatments for disease subsets or different stages of disease.

Similar to the recognition of **disease stages** as diseases, orphan drugs are increasingly being designated on the bases of **very specific patient subsets** and indications. Where previously breast cancer was considered the definition or description of the disease, specific mutations that form the spectrum of breast cancer are now being regarded as the description of the disease, and thus subsequently qualifying for orphan drug status.

Analysis of applications from 2011-2013 found that 28 of 72 orphan drugs were designated on the basis of a very specific indication or disease subset¹³. However, as targeted treatments become a greater priority for innovators, there is a question of whether these medicines should continue to be regarded as orphan drugs.

While the “slicing” of a disease into smaller subsets satisfies the current definition of a rare disease, consideration must be given to whether this approach is consistent with the intention of the orphan drugs policy.

C. A combination of A and B

Restricting orphan drug designation to whole diseases, rather than considering subsets, limited indications and disease stages, may reduce the number of orphan drug designations by the TGA.

On one hand, this would target the designation to drugs that are potentially of lowest financial viability, but on the other hand, this approach could be seen to create a very restrictive orphan drugs program, which may be out of step with other international regulators.

Furthermore, based on the recent designations, such an approach may have a limited impact on the overall number of orphan drug designations.

It could also be argued that as medicine evolves and targeted treatment becomes a higher priority considering diseases stages, subsets and restricted indications as the disease may be compatible with the original intention of the orphan drugs program – to provide patients access to medicines they may otherwise not be able to access.

D. Retain the status quo

Currently the Australian definition for an orphan drug is largely consistent with other regulators, i.e. it is an orphan drug is a medicine intended to treat a rare disease. Differences between regulators arise from differing patient thresholds (discussed in Section 3 and below), definition of a ‘rare disease’ and the seriousness of the disease. From the description in Section 4 of the EMA and FDA Orphan Drug programs, it could be argued that the definition is sufficiently consistent with others that further harmonisation is not required. Further, this consistency may suggest that the current Australian definition adequately captures the intended patients.

In light of the increased focus on targeted medicine, and the small patient populations that this will entail, the current definition could be regarded as adequate for the current situation and the evolving market.

Retaining the current definition will allow targeted treatments that will only be used by a small patient population to continue to be recognised as orphan drugs.

¹³ Being a rare disease was of itself not sufficient to be counted here. 11 of the 18 designations on the basis of the stage of the disease being treated (as above) also met one or other of the criteria that it was a very specific indication or disease subset. 7 of the 18 were not also counted here because their criteria for inclusion in the stage of disease being treated depended only on past treatment failure or intolerant of other therapies. In addition a further 17 designations were for a very specific indication or disease subset.

Patient threshold

A. Consider a new threshold

The current definition requires that an orphan drug is used in not more than 2000 people at any time. This is considerably lower than the population limits used by the EMA and SwissMedic, (5 in 10,000) and most other orphan drug programs looked at, see Table 2 for comparison.

The average prevalence threshold is around 5 in 10,000 with Australia being comparably very low at 0.88 in 10,000 and Singapore very high at 37.7 in 10,000. On the basis of this comparison it would appear that the current Australian definition is very low and may require reconsideration.

This figure should arguably be reconsidered in light of the population growth since the program began. For example the threshold could be expressed as a percentage of the population to better reflect population growth rather than a static number, or as prevalence of disease per 10,000 people, as is commonly done in other programs. Please refer to Section 3 for further discussion of this issue.

If there are any changes to definition or a charging model is introduced which may affect the utilisation of the orphan drugs program, increasing the patient threshold may be useful to ensure that the intended patients of the program based on the original policy objective of the program are not adversely affected.

B. Retain the status quo

Despite the prevalence threshold for orphan drug designation in Australia being comparatively low, there has not been significant pressure or requests to increase the patient threshold and increasing the patient population would potentially result in increased numbers of orphan drug designations. It could thus be argued that the current threshold is adequate and no change is required.

Charging model

The current fee waiver policy was intended as an incentive to bring products to market for a small patient population and there was little financial incentive to do so.

However, the “new orphan” drugs paradigm has seen a shift in pharmaceutical development more towards ‘orphan’ indications. Companies are focussing more on developing treatments for a small population within one country, but globally will have a substantial patient population, particularly for cancer subsets and disease phases. These medicines usually come at a considerable cost to patients, or governments and insurance companies, and even in modest patient populations can generate significant turnover for the commercial sponsors. With this in mind, together with the costs being incurred by the TGA to deliver the orphan drug program (Section 3) – which because of TGA’s full cost recovery model in effect are shifted onto other sponsors, including companies that do not supply orphan drugs - the question must be asked whether a total fee waiver is necessary to ensure these medicines are available in Australia.

The table below (Table 8) shows the distribution among sponsors of currently designated orphan drugs, and provides an indication of how some companies are shifting their market priorities towards orphan drug/targeted treatments.

Table 8: Number of orphan drugs per sponsor (data from <http://www.tga.gov.au/orphan-drugs>)

Number of designated orphan drugs	Sponsor/s
20	Novartis Pharm
13	Baxter Healthcare Pty Ltd
11	GlaxoSmithKline Australia Pty Ltd, Orphan Australia
10	Genzyme Australasia Pty Ltd
9	Roche
7	Novo Nordisk
6	Actelion, Celgene Pty Ltd, CSL, Janssen-Cilag, Pfizer Australia Pty Ltd, Pharmacia Australia, Schering Plough, Wyeth
5	Link Pharmaceuticals (Link Medical Products), Merck Sharp and Dohme, Ophtalmic Laboratories
4	Delpharm, Fresenius, Gilead Sciences Pty Ltd
3	Alexion Pharmaceuticals Australasia Pty Ltd, Amgen, Aventis Pharma, Bayer, Biogen Idec, Boehringer Ingelheim Pty Ltd, Cedarglen Investments, Eli Lilly, Glaxo Wellcome, Phebra Pty Ltd, Sanofi-Aventis, Shire
2	Abbott Australasia Pty Ltd, AbbVie Pty Ltd, Astra Zeneca, Ballia Holdings, Daval Australia Pty Ltd, Emerge, Hospira, Ikaria, Invida Australia Pty Ltd, Ipsen Pty Ltd, Kendle, Merck Sereno, Nycomed, Pharmacia and Upjohn, Pharmalab Pty Ltd, Pharmion Pty Ltd, Rhone-Poulenc Rorer
1	Abraxis Bioscience, ANSTO, Ariad, Avax, Aza Research, Bausch and Lomb, BioMarin, Bioregulatory Consulting, Biotech Regulatory Solutions, Bristol-Myers Squibb, Ciba Vision, Clinical Network Services Pty Ltd, Clinuvel Pharmaceuticals Ltd, Douglas Pharmaceuticals, Dutec Diagnostics, Ferring Pharmaceutical, FH Faulding, Gambro, Hoechst Marion Roussel, Icon Clinical, Medical Dynamics, Microfarm, Mrs Aleksandra Harasemcuk, Mundipharma, Nitecs, Norgine, Omnicare, Organon, Orpharma, Pathogenesis Corporation, Pharmaxis, Pierre Fabre Medicament, PPD Australia Pty Ltd, Rhinoscience, Sanofi-Synthelabo, Schering Pty Ltd, Searle, Sereno, Siena Biotech Italy, Specialised Therapeutics Australia Pty Ltd, Trimed, UCB Pharma, Vertex, Voisin Consulting

A. Initial registration free, fees payable for all subsequent changes

To continue providing incentive to sponsors to bring orphan drugs to market, the initial evaluation and registration of a designated orphan new chemical entity could continue to have fees waived. However, all subsequent changes (i.e. additional indications) to the originally designated orphan NCE would be subject to fees and charges.

This would include fees for additional/extension of indications which result in separate and distinct goods under the Act, as well as all other changes and variations, as well as generic products.

This option may encourage sponsors to submit multiple indications at the time of initial registration, potentially improving medicine availability for patients. However, it may also result in a delay to market as sponsors seek to gather the evidence required for all indications, which would not benefit patients or sponsors.

Alternatively, this approach may result in products being used off-label¹⁴.

A review of the orphan drug applications for 11/12, 12/13 and 13/14 suggests this approach would still result in considerable cost to TGA as most of the cost for the orphan drug program is the result of new medicines, and not variations. The costs for these activities are in Table 9 below.

Table 9: Fees foregone for orphan drug evaluations for new chemical entities and variations

	11/12 (# applications, \$ value of fees forgone)	12/13 (# applications, \$ value of fees forgone)	13/14 (# applications, \$ value of fees forgone)
New Chemical Entities	10, \$2,162,000	21, \$4,300,000	12, \$2,500,000
Variations	9, \$740,990 Extension of indication=5 Major variation= 1 Minor changes = 3	17, \$1,600,000 Extension of indication=10 New generic = 2 Major change= 2 Minor changes = 3	19, \$1,030, 000
Total (#applications fees)	19, \$2.9m	38, \$5.9m	31, \$3.53m

*New generic is an application for a generic prescription medicine.

The figures are calculated based on the date the application was received by the TGA as that is when fees are payable. The application may be complete or still in progress at 1 May 2014. The \$ value of fees foregone is based on fees and charges payable are as set out in the [Summary of fees and charges, July 2014](#).

¹⁴ The issue of off-label use and the delay or resistance to adding additional indications to registered medicines is common to all prescription medicines

B. Reduced fees for designated orphan drugs

To continue to provide incentive to bring medicines for rare diseases to market in Australia, a reduced registration fee for designated orphan drugs could be applied. It is proposed that this reduction could be 50% of the evaluation and registration fees for non-orphan drugs.

This proposal would still provide financial incentive to sponsors to register these medicines, but would also improve the financial sustainability of the orphan drugs program as the number of designated orphan drugs increases over time.

This proposal could be applied either as:

- A 50% reduction for initial registration fees and subsequent variations to the ARTG entry and annual fees; or
- A 50% reduction only on initial registration fees, with all subsequent variations to ARTG entries and annual fees charged at the full rate.

If this is the preferred approach consideration needs to be given to a corresponding reduction of fees and charges for non-orphan prescription medicines that currently effectively cross-subsidise the orphan drugs program.

C. Abolish the fee waiver for orphan drugs

The savings to sponsors through fee waivers were intended to provide an incentive to bring these products to market. However, it could be argued that the cost of evaluation in Australia is minor in comparison to the cost of the research and development of the drug, and that the TGA fee waiver makes little difference to the overall viability of bringing a medicine to market.

For a product with a new chemical entity or new combination of active ingredients the TGA fee for evaluation in 2014/15 is \$221,400. It is difficult to quantify the extent the orphan drugs program has contributed to supporting the development and supply of these drugs to market in Australia, and whether the existence of the scheme has led to any particular medicines being submitted for market authorisation that otherwise would not have been made available on the Australian market.

It is also difficult to predict whether there would be a disincentive to bring medicines to market in Australia if some level of fees for evaluation were imposed. Sponsors primarily recoup the cost of research and development through pricing, potentially making a fee waiver of limited potential financial benefit.

If evaluation fees are not a true barrier to bringing these products to market in Australia, the option of abolishing the current fee waiver could be considered.

To ensure small population groups with rare diseases, for example paediatric patients or other specific demographic groups, are not adversely affected by this option, specific circumstances and criteria could be developed for when a full or partial fee waiver could be granted for a designated orphan drug.

Again if this option were implemented, consideration needs to be given to a corresponding reduction of fees and charges for non-orphan prescription medicines.

D. Retain the status quo

The final option for a charging model is to not make any changes to the current arrangements and to continue to absorb the cost of the orphan drugs program through the registration fees of prescription medicines.

Possible reform packages

While – apart from maintaining the status quo - there are many potential options for reform in the definition, patient threshold and charging threshold for assessment for market authorisation of orphan drugs – these issues are interactive. Four combinations of options are proposed for further consideration. Subject to further consultation, the cost or savings impacts would be assessed in detail in a RIS but some brief summary of expected impact on numbers of patients or drugs affected and impacts on TGA fee recovery are made below.

Option one

- Definition – D Retain the status quo
- Threshold – A Increase the patient threshold
- Charging model – A Initial fee waiver, but all subsequent fees applied.

Definition – this option allows for the current trend in targeted treatments to continue to be recognised as orphan drugs.

Threshold – increasing the patient threshold to better reflect the population as it grows addresses concerns that people with traditional rare diseases may be missing out on treatment.

Charging model- an initial fee waiver provides an initial incentive to get orphan NCEs registered, but reflects the changing market focus for these medicines and the cost-recovery obligations of the TGA.

An initial analysis suggests that this may provide access to a larger number of patients, with no change to the range of medicines designated as orphan drugs, and have an overall neutral impact on fees forgone by TGA.

Option two

- Definition – A Restriction of disease stages
- Threshold – A Increase the patient threshold
- Charging model – A Initial fee waiver, but all subsequent fees applied

Definition – restricting access to the entire disease life, rather than specific stages will reduce the overall number of orphan drug designations, although not significantly. It could be argued that defining a disease by stage is not in the spirit of the objectives of the orphan drugs program, especially as many disease sufferers can expect to reach “last line” treatment stage regardless of the overall disease incidence.

Threshold – increasing the patient threshold to better reflect the population as it grows addresses concerns that people with traditional rare diseases may be missing out on treatment.

Charging model- an initial fee waiver provides an initial incentive to get orphan NCEs registered, but reflects the changing market focus for these medicines and the cost-recovery obligations of the TGA.

An initial analysis suggests that this may provide access to an increased number of patients, but for a more limited range of medicines, and have an overall neutral impact on fees forgone by TGA.

Option three

- Definition – D Retain the status quo
- Threshold – A Increase the patient threshold
- Charging model – C No fee waiver except in specific circumstances

Definition – this option allows for the current trend in targeted treatments to continue to be recognised as orphan drugs.

Threshold – increasing the patient threshold to better reflect the population as it grows addresses concerns that people with traditional rare diseases may be missing out on treatment.

Charging model – While the overall impact of the orphan drug program fee waiver is difficult to quantify, when compared to global sales for many orphan drugs, the fees for evaluation and registration are relatively small and could arguably make little difference to the overall viability of a proposal to seek registration. If fee waivers in specific circumstances are to be included, careful consideration and clearly defined criteria would need to be crafted to ensure this adequately reflects the objectives of the orphan drugs program.

Option four

- Definition – D Retain the status quo
- Threshold – A Increase the patient threshold
- Charging model – B Reduced fees for designated orphan drugs.

Definition – this option allows for the current trend in targeted treatments to continue to be recognised as orphan drugs.

Threshold – increasing the patient threshold to better reflect the population as it grows addresses concerns that people with traditional rare diseases may be missing out on treatment.

Charging model – reduced fees for designated orphan drugs allows the TGA to fulfil its cost-recovery obligations with a growing orphan drugs market while still providing sponsors with an incentive to bring these medicines to market.

An initial analysis suggests that this may provide access to an increased number of patients, but for a more limited range of medicines, and have an overall neutral impact on fees forgone by TGA.

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Reference/Publication #