Thank you for the opportunity to provide stakeholder input for the above review. We commend the TGA for conducting a review of the Orphan Drugs Program. We recommended a review of the orphan program as part of our submission to the Review of Medicines and Medical Devices Regulation\(^\text{1}\), not aware that a review was already underway.

BioPharma Strategic Regulatory Services specialises in providing regulatory and strategic drug development advice and services for prescription medicines, including those developed by the Australian biotechnology sector. We are currently assisting in the designation and registration of orphan drugs for clients and have a significant depth of experience with orphan drug programs in Australia as well as the EU and USA.

Being consultants for the pharmaceutical industry, it would not be appropriate to make recommendations on any of the possible reform packages being proposed. However, in this submission, we have tried to highlight some important points for consideration and strongly believe the TGA should continue to provide assistance to encourage the marketing of orphan drugs.

In order to review the effectiveness of a program, we believe first and foremost, that one must determine whether the program is achieving its goals or not. In this case, has the Orphan Drugs Program provided sufficient incentive to sponsors to market medicines in Australia which would otherwise have been considered commercially unviable? We are unsure if this is apparent in the current review.

Under “Utilisation of the program”, the observation is made that 287 orphan designations were granted (by late 2013) and the number per year increased from 14 in the period 1998/99 - 2007/08 to 27 in the period 2008/09 – 2012/13. The comment is made in a number of places in the review that there appears to be a shift in pharmaceutical development towards orphan drugs. The review also highlights that approximately $35 million in potential fees were forgone since the commencement of the program. These are very high level findings and we believe some context should be provided.

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1. Number of Orphan Designations

The aim of the program is to encourage sponsors to market medicines for rare diseases, and therefore the increase in orphan designations should be seen as a positive result. Also, the number of designations is only part of the picture. One should consider the number of approvals generated by the designations.

This information is not readily available. Until recently, registration of orphan drugs was indicated in the TGA’s Orphan Drug Designation webpage but updating of this information did not always occur after registration and now appears to have been removed completely. However, BioPharma Strategic Regulatory Services has developed a database of all AusPARs since their inception in 2009. According to our database, 39 applications for new orphan drugs have been approved since 2010 (no orphan drug approvals were found for 2009). In the table below, we have presented the number of orphan as well as non-orphan drug approvals over this period.

<table>
<thead>
<tr>
<th></th>
<th>2010</th>
<th>2011</th>
<th>2012</th>
<th>2013</th>
<th>2014*</th>
</tr>
</thead>
<tbody>
<tr>
<td>New orphan drug</td>
<td>9</td>
<td>0</td>
<td>7</td>
<td>13</td>
<td>10</td>
</tr>
<tr>
<td>New non-orphan drug</td>
<td>20</td>
<td>23</td>
<td>16</td>
<td>23</td>
<td>19</td>
</tr>
<tr>
<td>All new drugs</td>
<td>29</td>
<td>23</td>
<td>23</td>
<td>36</td>
<td>29</td>
</tr>
</tbody>
</table>

* The 2014 column is greyed as the number of new drugs may not be complete; the most recent AusPARs (published as of 22 April 2015) continue to cover applications for which TGA decisions were made in 2014.

It can be seen that although there is a small increase in the number of orphan approvals since 2010, there is no indication of a "shift" from non-orphan to orphan drugs from 2010 to 2013. In addition, the number of orphan approvals are in line with the USA where there have been an average of 14 new orphan drugs approved yearly in the last two decades. Although it is difficult to compare drug approvals between countries, it would appear the Australian Orphan Program is achieving its goals. To give a picture of the rare diseases for which orphan drugs have been approved between 2010 and 2014, we have provided a table in Appendix 1 – based on the data captured in our database.

2. Forgone Fees

Although $35 million is substantial, it should be highlighted that no revenue has been forgone by the TGA as the agency operates according to a cost recovery model and therefore the sponsors themselves have been subsidising the orphan program to date. When outlining possible reforms, the review includes phrases such as “considerable cost to the TGA” and “fees forgone by TGA”. However, in reviewing the reform options, it is important to bear in mind that sponsors and not the TGA or tax payers will be impacted.

REFORMS

ORPHAN DRUG DEFINITION

Patient Threshold

The patient threshold for orphan designation in Australia (of 2,000 patients or 0.88 in 10,000) – as reported in Table 2 – is the lowest amongst the countries/regions. There is therefore a clear need to redefine the threshold. It is recommended to define the prevalence as proportion of the population – instead of the current static absolute figure – to account for changes in total population; and to increase the threshold to 5 in 10,000 as per other comparable economies. One should remember that

even if registration is achieved for the population covered in the designation, not all patients will be treated; and this is further impacted by restrictions often imposed by the PBAC which can greatly reduce the eligibility of patients for treatment and thereby effectively reducing the population who will receive the medicine.

Furthermore, an increase in the patient threshold may have an impact on some of the other findings in the review such as the authors’ perception of an increasing reliance on designation for disease subsets – see below.

**Disease stages or subsets**

It could be argued that the low current prevalence threshold for orphan drugs has been the reason for the “very narrow” orphan designations of late – as highlighted in Table 4 of the review. In the case of the 4th example, ramucirumab (designated for treatment of patients with advanced gastric cancer or gastro-oesophageal junction adenocarcinoma after prior chemotherapy), this drug was given orphan designation by the EMA for the entire population of patients with gastric cancer; As outlined in the EMA’s Public Summary of Opinion, the prevalence was reported as 3 in 10,000.

The review makes specific mention of oncology drugs as a class where there is an increasing trend in restricting orphan designation to disease stages and subsets. However, one needs to take into consideration the benefit-risk profile of each medicine. Many chemotherapy treatments – due to their toxicity – may only achieve a favourable benefit-risk profile in the more advanced stages of treatment, and may never be utilised earlier in the course of the disease.

**The new orphan drug paradigm**

As noted in the review, there has been an increase in highly specialised medicines for smaller population groups. However, this must be seen as a positive trend as more targeted treatment should potentially result in increased efficacy and/or safety when used in the correct patient. If the resulting patient numbers is such that less than 5 in 10,000 would be eligible, then orphan programs would ensure sponsors continue to develop these treatments as they may not otherwise be commercially viable.

In the case of the 3rd example in Table 4, drisapersen (designated for treatment of patients with Duchenne muscular dystrophy (DMD) bearing certain mutations that are amenable to treatment with exon 51 skipping), it should be noted that the prevalence of DMD – regardless of mutation – has been calculated to be 1.51 in 10,000. Therefore, as with ramucirumab, drisapersen would also be eligible for orphan designation for the entire DMP population if the prevalence was lifted to 5 in 10,000.

**CHARGING MODEL**

The review lists a number of reforms and a qualification is given that further consultation will follow to ascertain the impact of the cost or savings from the reforms. In addition to considering feedback from other stakeholders on the effectiveness of the orphan program and how it may be improved, it is crucial to actively seek input from all sponsors in the industry as it will be the sponsors who will be affected by any changes in fees.

In Option B: Reduced fees for designated orphan drugs, there is mention made of consideration being given to a corresponding reduction in fees for non-orphan applications that are currently cross-subsidising the orphan drugs program. Sponsors need to be able to determine the overall impact of any charging reforms in the orphan program to their regulatory costs for their entire product portfolio. It is difficult to estimate the resulting reduction in these fees as we are not privy to the model used to cross-charge sponsors of non-orphan applications. However, we have attempted to calculate a

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4 Public summary of opinion on orphan designation, EMA, dated 3 March 2015,

possible fee reduction, based on the figure of $3.53 million reported in Table 9 for the total value of fees forgone by the TGA in 2013/14.

Firstly, we need to determine the total revenue received by the TGA from sponsors. This revenue is reported separately in the 2014 Cost Recovery Impact Statements for all TGA sections: Blood, blood components and biologicals (human cell and tissue therapies), Complementary medicines, Good manufacturing practice, Medical devices, Over the counter medicines and Prescription medicines. Based on the estimated revenue reported in each statement, the total fees received from sponsors in 2013/14 was $128.9 million. If the fees for orphan applications were abolished or reduced by 50%, and the regained fees equally re-distributed across the total fees received (assuming no change in the total number of applications), this would result in a reduction of 2.67% or 2.70%, respectively.

Any potential savings in non-orphan application fees needs to be considered alongside the potential disincentive for sponsors of orphan drugs – many of which are small companies, including Australian start-ups eg Prana Biotechnology (Huntington’s chorea), Novogen (ovarian cancer) and Pharmaxis (cystic fibrosis). Any assistance by way of fee waiver (or other incentives – see below) would help to ensure the continued development of these drugs. Even in the case of large multi-nationals, business cases need to be made before proceeding with marketing applications in Australia. There are always risks involved in launching new medicines, more so with orphan drugs due to the very limited population, particularly considering any new competitor would have a very significant impact on commercial return. For this reason, we would recommend the consideration of some form of market exclusivity for orphan drugs.

Further, as Australia’s population is small relative to the majority of international markets, the return on investment is usually less than in other countries. A waived evaluation fee provides considerable inducement for sponsors to market their medicines in Australia sooner rather than later.

We would like to close with consideration of the impact of the forgone fees taken into context with the TGA’s total revenue and expenditure (i.e. beyond the fees received and expenditure on evaluations). Based on the results reported in recent Financial Statements for 2013/14 released by the TGA, total revenue was $133.60 million (anticipated) and expenditure was $137.33 million (actual). This means that if the anticipated revenue for 2013/14 was realised, then the TGA’s budget had a surplus of $3.73 million – greater than the $3.53 million cost of the orphan drug program. Therefore, all signs indicate the orphan program is not having significant impact on the TGA’s budget while providing incentive to sponsors to market orphan medicines which they may otherwise have not, or as soon. We believe the prevalence threshold for orphan drugs can be improved to provide further incentive as well as possibly reducing the perceived trend in designations for disease subsets.

Thank you again for the opportunity to provide stakeholder input into this review.

Yours sincerely

BioPharma Strategic Regulatory Services

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7 TGA Business Plan 2013/14, Therapeutic Goods Administration, dated 19 December 2013
8 TGA Business Plan 2014/15, Therapeutic Goods Administration, dated 26 November 2014