Overall Comment

GSK is highly supportive of all rare disease and orphan drug initiatives and incentives to bring much needed medicines to patients with rare diseases.

GSK is appreciative of the transparent, open and diligent consultation by the TGA of its Orphan Drugs Program. It is acknowledged that there are challenges faced by the Agency in addressing all the issues and suggestions raised in response to the 2015 consultation and recognition that the Agency has developed a robust proposal on which to offer incentive to developers of drugs for rare diseases that will put rare disease patients first. Although the Agency has not proposed additional incentives, such as market exclusivity/tax credits, at this time, it is hoped that the TGA will continue to consider such opportunity in the near future.

Specific Comments to the Consultation Questions

Stakeholders are invited to comment on six consultation questions.

Please specify:

- whether or not you support the proposed changes to the TGA orphan program. If you do not support the change/s, you may make suggestions for an alternative.
- an assessment of how the proposed change will impact on you, and what you see as the likely benefits or costs to you (financial or non-financial).
- if possible, please attempt to quantify these costs and benefits.

Consultation item 1 – rare disease threshold, seriousness of the condition

A rare disease threshold of 5/10,000 (approximately 12,000 Australians) is proposed as one of two acceptable conditions for orphan designation. This is numerically less restrictive than currently (2000 Australians) and in isolation would allow more diseases to qualify as rare. In addition, the seriousness of the condition will be introduced as a new criterion for orphan designation, such that only conditions that are life threatening or chronically debilitating will qualify. The second and current option for sponsors to seek orphan designation based on a lack of financial viability independent of the rare disease threshold is proposed to be retained for conditions that are life threatening, seriously debilitating or serious and chronic. (Question 1, page 14)

GSK Comment on Consultation item 1 – rare disease threshold, seriousness of the condition

- GSK supports the proposed change. GSK supports raising the extremely low threshold of “not more than 2000 individuals in Australia” to a prevalence basis of 5 in 10,000, which addresses population growth and bringing the limitation in line with other major regulators. GSK also supports the more defined patient population with high unmet
medical need, i.e. a rare disease as any disorder or condition that is life-threatening or a chronically debilitating disease.

- This proposed change will impact GSK by potentially increasing the number of orphan designations sought in Australia ahead of filing marketing authorisation application (MAA). GSK envisages the likely financial benefit for additional fee waivers.

**Consultation item 2 – existing treatment and significant benefit over existing treatment**

The proposed orphan program introduces new criteria that aim to bring orphan products to market that treat conditions for which there is no existing treatment, or that can provide significant benefit over existing treatments. In this context, existing treatments would be established based on the Australian standard of care. If there are existing methods of treatment, the application must be supported by a justification of significant benefit over such treatments. Significant benefit can be demonstrated based on an assumption of improved efficacy, improved safety or a major contribution to patient care. (Question 2, page 14)

**Consultation item 2 – existing treatment and significant benefit over existing treatment**

- GSK supports the proposed change to introduce the new criteria of existing treatment and significant benefit over existing treatment to the TGA orphan program. GSK recognises and welcomes the proposed change on the basis that it balances the increased threshold to ensure that the scheme remains financially viable. The proposed change supports bringing much needed innovative therapies to patients with rare diseases.

  GSK also supports that “significant benefit can be demonstrated based on an assumption of improved efficacy, improved safety or a major contribution to patient care”.

- This proposed change will impact GSK by adding the complexity/burden of preparing a justification specifically addressing the Australian standard of care to the orphan drug designation application ahead of marketing authorisation application. Additional time and resource will be required to prepare such a justification. After the last consultation in 2015 it was suggested that an approved EU orphan drug designation could be adopted by the TGA to grant an Australian orphan drug designation. It was expected that Australian epidemiology data or possibly a truncated application would still be required. It is disappointing to see that this is not being considered by the TGA in this current consultation.

**Consultation item 3 – orphan condition, medical plausibility and biomarkers**

Where the proposed orphan medicine is intended for only a subset of persons with a disease or condition, the TGA currently requests a justification of the medical plausibility as to why the remaining persons with the same disease or condition are not appropriate candidates for use of the medicine. The concept of medical plausibility is proposed to be retained. The distinct condition is proposed, in alignment with EMA criteria, to be defined in terms of the specific characteristics, e.g. pathophysiological, histopathological, clinical characteristics. The genetic subtype/profile could additionally be included to define a subgroup. In general, subgroups would only be considered appropriate where the product would be ineffective or unsafe in the remaining population not having these characteristics. This applies equally where a biomarker is used to determine the subgroup. Defining a subset by reference to the fact that the drug will (or has) only been tested in a subgroup of patients would not be considered a sufficient justification for the restriction to a patient subgroup. (Question 3, page 14)
• GSK supports the proposed changes to define the distinct orphan condition in terms of the specific characteristics, e.g. pathophysiological, histopathological, clinical characteristics.

• The proposed change will unlikely impact GSK as we would make the same assessment and approach as for Europe.

Consultation item 4 – Paediatric populations

Paediatric indications will continue to be considered for orphan designation, where the prevalence criterion is met in relation to the whole of the disease, or where the disease is different in the paediatric subgroup, or specific to the paediatric subgroup. Subgrouping based on the age of the sub-population would only be considered appropriate where the product would be ineffective or unsafe in the remaining population. The change in the rare disease threshold is expected to increase the number of paediatric conditions that may receive orphan designation. Paediatric indications that are not eligible based on the rare disease prevalence may be eligible for orphan status based on a lack of financial viability (criterion 1). (Question 4, page 14)

Consultation item 4 – Paediatric populations

• GSK supports the proposed changes in accordance with Consultation item 1. GSK supports raising the extremely low threshold of “not more than 2000 individuals in Australia” to a prevalence basis of 5 in 10,000, which addresses population growth and bringing the limitation in line with other major regulators.

• GSK also supports the maintenance of the lack of financial viability criteria as an alternative way to qualify for orphan status.

• This proposed change will impact GSK by potentially increasing the number of orphan designations sought in Australia ahead of filing marketing authorisation application (MAA). GSK envisages the likely financial benefit for additional fee waivers.

Consultation item 5 – Modifications to the designation process

The key change to the designation process aims to align the timing of the assessment of eligibility for orphan designation closer with the date that the related registration application is lodged. The orphan designation is proposed to lapse within a set period, between 3 and 6 months of designation, if no registration application is lodged. This will ensure that the designation of orphan status is based on information that is current. Moreover, the designation can be withdrawn by the sponsor at any time. The TGA retains the right to cancel the designation at any time if there is evidence that the criteria for orphan designation are no longer met. (Question 5, page 16)

Consultation item 5 – Modifications to the designation process

• GSK does not support the proposed set period in which an orphan designation may lapse. Often, the preparation of a MAA may take longer than expected on review of pivotal data results or for other reasons, and so, there is a potential risk that the orphan designation obtained may have lapsed by the time of file. The TGA should consider extending the set period to at least 12m and/or to giving reassurance that the orphan drug designation application may be refiled such that orphan designation may be obtained prior to a delayed MAA file.

• This proposed change will impact the complexity of file planning and preparation at GSK.
Consultation item 6 – Other considerations

Are there any other key issues that should be considered in developing the changes to the orphan drug program? (Question 6, page 16)

Consultation item 6 – Other considerations

- Sponsors need confidence in obtaining the orphan drug designation ahead of a planned MAA file. Therefore, confirmation of medical plausibility, potential significant benefit and set period for a potential orphan designation is critical for a sponsor to know in advance of file, to be able to prepare for registration fees should they be required. This is acknowledged more as financial burden for small and medium Companies. GSK proposes that the Agency offer advice/consultation ahead of any planned application for orphan drug designation. Smaller Companies may appreciate the advice to support their drug development efforts.

- GSK would support a further TGA review of the Orphan Drug Program to consider the impact of the proposed changes if implemented at a set timepoint in the future, e.g. 2/3 years.

- Although the Agency has not proposed additional incentives, such as market exclusivity/tax credits, at this time, it is hoped that the TGA will continue to consider such opportunity in the near future.

- The analysis in box 3 predicts that there will be no major impact on the overall application numbers and program cost. The number of orphan application is also predicted to increase in coming years. Therefore, although the TGA are not proposing changes to the fee structure at this time, the introduction of small application fees for orphan drugs may need to be considered to avoid significant increases in fees for other regulatory applications in the future.