Re: Consultation: Provisional Approval pathway for prescription medicines

We refer to the above consultation being undertaken by the TGA. We are providing our response to some of the questions raised in the consultation paper in the accompanying document.

We appreciate the opportunity to provide feedback to this important consultation.

Yours sincerely

SHIRE AUSTRALIA PTY LTD

David Tsui
Director, Regulatory Affairs

Encl.
Data requirements for the registration application

Q1. Do you envisage any difficulties in providing prospective advice on timelines for submission of clinical data?

Shire response

In developing novel medicines for treating rare diseases, and in particular those with an extremely low prevalence, it is often more difficult to predict with a high degree of certainty the timeline for completion of clinical studies for a variety of reasons.

The lack of good information on the natural history of a rare disease often creates a significant challenge for determining the appropriate duration of follow up of clinical meaningful endpoints. This aspect is compounded further by the heterogeneity of patient populations with variable phenotypes and clinical courses. Besides being affected by the eligibility criteria of the clinical study, available patients in small numbers are geographically dispersed, and they are often managed by multiple specialties due to comorbidities. All these factors add to the logistical complexity of clinical study execution making accurate prediction of the timeline of data availability more difficult.

Shire believes it is important for sufficient flexibility to be introduced in the proposed Provisional Approval process to allow a sponsor to justifiably renegotiate where necessary the timing of provision of additional confirmatory data.

Factors influencing our decision-making

Q3. Are there other factors that should be taken into account to inform the registration decision for Provisional Approval?

Shire response

Orphan drugs

Shire is of the view that medicines with orphan drug designation should qualify for the going through the Provisional Approval pathway should the company choose to use this route of registration. This is consistent with the European Conditional Marketing Authorisation (CMA) process whereby orphan medicinal products fall within the scope of CMA. [1]

Re-routing of an application from standard registration to Provisional Approval registration pathway

Shire believes the Provisional Approval pathway should include the option actionable by the TGA, after consultation with the sponsor, to re-route an application submitted through the standard registration pathway to the Provisional Approval registration pathway during the pre-market assessment phase.

With the CMA process currently operating in the EU, there is the option for the CHMP, after consultation with the applicant, to propose granting CMA to a new medicinal product for which the applicant did not request CMA at the time of filing a marketing authorisation application. Such an option is not being made available in the TGA’s proposed Provisional Approval pathway.

According to a report by the EMA on their ten years (2006 to 2016) experience of granting CMA, 53% (16/30) were granted after negotiation during the review between the EMA and the applicants rather than the CMA being requested by the applicant at the time of initial submission. Such statistics suggest that a fair proportion of applicants held the view the data contained in the submitted dossier were sufficient to support full marketing authorisation. Although the CHMP did not come to the same conclusion about the completeness of supporting data, the committee still decided that the overall benefit-risk balance of the medicines was positive enough to propose granting of CMA with specific obligations.

Shire believes the option of re-routing an application from the standard registration to the Provisional Approval registration pathway during regulatory review (i.e. without prior designation) should be included as a part of the new process. This is in keeping with the three objectives of expedited pathways i.e. (a) to assist in achieving earlier access to novel medicines that address unmet clinical needs; (b) provide timely and flexible registration processes for sponsor seeking access to the Australian market for new and novel medicines that offer substantial benefits to Australian consumers; and (c) increase alignment with other overseas regulators that offer accelerated assessment processes.

Q4. Are there other factors that should be taken into account to inform the registration decision for Provisional Approval?

Shire Response

For reasons given in our response to Question 3 to justify inclusion of the option to re-route an application from the standard registration to the provisional registration process, we believe not having prior Provisional Approval registration designation should not be a sufficient condition to disallow the granting of provisional approval.

Conditions of provisional registration

Q5. Do you envisage any difficulties with the proposed requirement to collect and submit confirmatory data on efficacy and safety within the provisional approval period?

Shire response

Under the current proposal, the TGA expects a sponsor to provide evidence that planned clinical trials will be completed within the provisional registration period (a limited duration of 2 years unless the sponsor applies for full registration), taking into account of future extensions (a maximum of 2 extensions). Such proposed measures are presumably aimed at getting sponsors to expeditiously generate additional data to convert provisional registration to standard registration.

According to data contained in the EMA report on their 10-year experience in administering CMA, 11 out of a total 30 CMA granted were successfully converted into full MA over the 10-year period. It was also revealed it took an average of 4 years for the conversions to occur (median = 4.2 years; range = 0.48 to 7.1 years), and 3 of the 11 CMA (27%) took more than 6 years to convert.

Assuming the aforementioned sample of CMA granted in the EU is a fair representation of those that will receive provisional registration in Australia, about a third of these will likely be removed from the Australian Registry of Therapeutic Goods under the current proposal of a maximum provisional registration period of 6 years (i.e. a 2-year provisional registration period with a maximum of two extensions). The continued accessed of these medicines by patients will be primarily through the Special Access Scheme which does not involve regular reappraisals of benefit-risk balance by the TGA.

In contrast, there is no time limit imposed by the CHMP/EMA on CMA. Instead the marketing authorisation holder is required to renew the CMA on an annual basis by submitting documentation which includes an interim report on the progress of fulfilment of specific obligations and relevant information to demonstrate the benefit-risk balance continues to remain positive.[1]

Shire recommends that, like the CMA process operating in the EU, no time limitation should be imposed on provisional registration on the condition that the sponsor is committed and able to submit documentation on an annual basis (or biennially to replace the proposed 2-year automatic lapsing of provisional registration) to demonstrate the benefit-risk balance continues to remain positive, and update the TGA on the progress of on-going clinical studies and interim results.

**Q6. What factors should be taken into account when determining whether the sponsor’s proposal for collecting confirmatory data is sufficient?**

**Shire response**

The TGA has indicated in the consultation document that it will apply provisional registration conditions that are consistent with those imposed by comparable overseas regulators if they are relevant and applicable to Australia. Shire supports this approach.

**Lapsing or extending provisional registration**

**Q11. Do you envisage any difficulties with the proposed automatic lapsing after a two year period?**

**Shire response**

Please see Shire’s response to Q5

**Q12. In what circumstances do you envisage that an extension to the provisional registration period will be sought?**

**Shire response**

As mentioned in our response to Q1, the logistics of running a clinical trial to study a rare disease is logistically more complex due to rarity of the condition. Therefore it is envisaged that medicines developed for treating rare disease are more likely to have the need to extend the provisional registration period in order for the planned post-approval clinical studies to be completed.

With the continuous advancement of medical technology and knowledge, there is also the possibility of the introduction of new or a change to internationally recognized treatment guidelines for a medical...
condition. This scenario could affect the choice of the primarily clinical endpoint(s) and study design necessitating protocol amendment and extension of the study duration.

Q13. **Under what circumstances should the TGA consider a modification of conditions or undertakings for provisionally registered medicines?**

**Shire Response**

Since provisional approval pathway is meant for accelerating the introduction of medicines developed for serious medical conditions with unmet clinical need, the primarily consideration must be focused on the access of such medicines by patients. In this regard, the TGA should be able to consider a sponsor's request to negotiate modification of conditions or undertakings with justifications. Please see also our response to Q12.

**Legislative and regulatory amendment**

Q15. **Do you support the proposed amendments to limit appeal rights to certain TGA decisions and to the sponsor only?**

**Shire response**

Shire agrees with the TGA proposal that appeal rights be limited to the applicant/sponsor.

**Other feedback on the Provisional Approval pathway**

Q16. **Is there anything else you would like to raise that has not been covered in this consultation paper?**

**Shire response**

Shire recommends the TGA consider also adopting an additional approval pathway similar to the marketing authorisation granted under “exceptional circumstances” in the EU.

The current EU regulator regime includes a pathway for granting marketing under “exceptional circumstances” in the absence of comprehensive data. As distinct from CMA, comprehensive data are not expected to be obtained even after marketing authorisation, and such pathway generally will not be converted to standard marketing authorisation. An example would be a medicine developed for treating an ultra-rare disease such that the applicant cannot reasonably be expected to provide comprehensive data. [4]

---

4 Annex I Part II of Directive 2001/83/EC
http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/q_and_a/q_and_a_detail_000167.jsp&mid=WC0b01ac0580b18196