GSK Comments on TGA Consultation
Provisional Approval pathway for prescription medicines:
Proposed registration process and post-market requirements
(Version 1.0: March 2017)

Overall Comment

GlaxoSmithKline (GSK) welcomes the opportunity to comment on the TGA consultation *Provisional Approval pathway for prescription medicines* in relation to prescription medicines.

GSK is appreciative of the transparent, open and diligent consultation by the TGA in an effort to streamline existing TGA assessment and registration processes and improving timely access to new medicines without compromising on Australian public health. GSK also appreciates the TGA's invitation to attend their workshop with a comprehensive group of stakeholders to discuss key areas.

Overall, GSK supports the TGA's proposal to introduce a provisional approval pathway to allow certain promising new medicines and new uses for existing medicines to reach patients with unmet clinical needs earlier than might otherwise be the case. However, further consideration is required to ensure that this pathway is flexible enough to accommodate the uncertainties associated with the completion of confirmatory clinical studies.

Specific Comments to the Consultation Questions

In response to this TGA consultation document, stakeholders were invited to comment on sixteen specific questions. Where GSK has a particular response to one of these questions, we have included this below preceded by the specific consultation question.

Data requirements for the registration application

Q2. Do you envisage any difficulties in providing prospective advice on timelines for submission of clinical data?

GSK Comments

- The provisional approval pathway envisages a "designation" phase. One of the criterion is: "...there is promising evidence from early data indicating that the medicine is likely to provide a major therapeutic advantage in efficacy and/or safety over existing treatments that are fully registered in Australia..."
- From the consultation document, it is unclear how comprehensive (or limited) the data package can be at this 'designation' phase. Early-phase clinical data can often appear "promising", but this is just the first hurdle in the provisional approval pathway which Sponsors have to negotiate. The second hurdle is focused on the availability of confirmatory clinical study data, and while estimated plans may be in place, it can be difficult to determine when such data will be available.
- Given the previous comment, it may be challenging to obtain confirmatory clinical study data with 2 years. If comprehensive confirmatory data is expected to be provided within 2 years of grant of provisional approval, Sponsors may be discouraged from seeking provisional approval, which would limit the benefits of such a scheme. Alternatively, although not mutually exclusive, TGA could consider accepting data as a rolling submission on a case-by-case basis. To aid this rolling submission process, Sponsors could

consider sharing with the TGA during the designation phase the provisional dates about when they are expecting to receive any supporting confirmatory clinical study data.

Factors influencing our decision-making

Q3. Are there other factors that should be taken into account during the dossier submission and evaluation phase for Provisional Approval applications?

GSK Comments

- The TGA consultation document does not appear to comment on whether the TGA will be taking into account the decisions and assessment of data by other regulatory authorities when assessing an Australian Sponsor's provisional approval application.
- GSK is of the view that in order to make the evaluation timings for provisional approval applications more efficient, the TGA should be open to considering the assessment's of other regulatory agencies as part of its review of a Sponsor's provisional approval application.
- GSK also notes that this consultation document proposes that the pre-market registration process for provisional approval is to follow a similar internal evaluation process to the standard Prescription medicines registration process and be completed within current legislated timeframes. While the TGA notes that it is open to, on a case-by-case basis, Sponsors submitting clinical or other relevant data by way of a rolling submission, this will only be afforded to Sponsors who have prospectively discussed the additional data that will be generated post dossier submission and the proposed timeframes for submission of this data will need to be determined at the outset.
- Given the potential for overlap between submitting the provisional registration application and its evaluation time and data read-outs from confirmatory studies, GSK is of the view that rolling submissions may become the norm. Therefore, GSK suggests that the TGA reconsider the timelines being proposed in order to avoid the "inefficiencies and delays" mentioned in the consultation document, and to provide Sponsors with a more detailed description of the assessment process (including information about how "clock-stop" periods might be utilised when data becomes available to a Sponsor in the future).

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

GSK Comments

- GSK notes that the TGA has indicated that it will consult external expert(s) as needed to inform its decision making for a particular provisional approval application. However, it remains unclear from the consultation document whether Sponsors will be informed about who the consulted external experts will be and/or when the TGA will engage them.

Enhanced risk communication

Q8. What information, communication and education activities should be considered to inform health professionals and consumers about provisionally registered medicines and the implications for patients?

GSK Comments

- The consultation document appears to have limited information about how the TGA will keep interested parties (e.g. Sponsors, health professionals and patients) informed about changes concerning provisional registrations.
- To ensure all interested stakeholders are informed about the status of a provisional registration, GSK considers that it might be worthwhile for the TGA to revise the ARTG summary so that it lists the regulatory status/history of a provisional registration.
- GSK further notes the TGA's proposal to include statements in the Product Information (PI) and the Consumer Medicine Information (CMI) about a medicine's provision approval status. However, in order to keep the PI and CMI documents current, GSK suggests the TGA reconsider its requirement that these documents need to be provided in hard-copy, rather than electronically. This suggestion aligns with the TGA's proposal of a TGA-developed mobile/electronic device APP (showcased at a recent TGA workshop) that would allow healthcare professionals (HCPs) and patients easier and quicker access to a medicine's PI and/or CMI information.
- As the TGA is aware, Sponsors face a number of challenges in trying to keep a medicine's package leaflet up-to-date. One of these challenges is manufacturing lead time of a medicine the subsequent time required to incorporate these leaflets into the medicine pack.
- GSK considers that in allowing electronic prescribing documentation Sponsors will be able to keep this information up-to-date. This is particularly important in those instances where the TGA may have to suspend/revoke a provisionally registered medicine's status following the emergence of a new patient safety concern.

Tracking and enforcement of registration conditions

Q10. What information should be published on the TGA website about the progress of RMP commitments, including confirmatory efficacy studies?

GSK Comments

- GSK is of the view that the TGA should only publish the regulatory status of a provisional approved medicine on the Australian Register of Therapeutic Goods (ARTG) and/or TGA website rather than the Sponsor's progress in fulfilling any conditions of approval e.g. RMP commitments. This is because the publishing of information other than the status is unlikely to add any sufficient value to the public's knowledge about this provisionally approved medicine.

Lapsing or extending provisional registration

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

GSK Comments

- GSK considers that the 2-year lapse period envisaged with the provisional approval pathway is potentially unrealistic (even with the prospect of further extensions).
- GSK notes that in Europe, Sponsors utilising the European Medicines Authority's (EMA) Conditional Marketing Authorisation (CMA) application process took on average 4.75 years to transition from a CMA to a 'normal' medicine Marketing Authorisation. This is because some of the post-marketing requirements can take longer to complete than the maximum extension envisaged under the provisional approval pathway.
- GSK also notes that the EMA reviews and renews CMAs on an annual basis (where the benefit-risk profile remains positive). As part of this review process, the EMA also reviews any specific obligations on the Sponsor devised as part of its decision to grant this medicine CMA.
- Given the relatively short, 2-year provisional approval period, GSK envisages that medicines approved by this pathway will either:
    - have their licences lapse on a regular basis as conformational clinical studies will not be available; or
    - the associated post-market requirements for these medicines may not be as robust as it needs to be in order for Sponsors to be able to fit the tight provisional approval timelines; or
    - the numbers of provisional approvals will be small, because the TGA will only grant provisional registration to medicines where evidence of early benefit-risk profile is "compelling" rather than "promising" and/or post-marketing studies are nearing completion during the review phase and likely to rolled-out within 18 months of provisional approval being granted.
- In light of the above, GSK notes that in order for this provisional approval pathway to be successful, the TGA needs to be as flexible as possible in designing and implementing the provisional registration pathway to ensure that all medicines that meet the criteria are duly considered for provisional approval. For example, the EU CMA has not been used much for medicines outside of the oncology and infectious disease therapy areas (and this is something the EMA wants to redress).
- Further, GSK is of the view that provisionally approved medicines that are clearly benefiting patients (even if a narrow population) should not be removed from the market if the Sponsor is unable to transition to full registration within the time allowed. The views of medical professionals should also be sought in any decision to withdraw or revoke a provisional registration.
- Finally, the TGA could also assist Sponsors by advising in advance about when a particular provisional registration is set to lapse. This would enable both the TGA and Sponsors to

discuss this registration lapsing and determine on a case-by-case basis how and whether this should occur.

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

GSK Comments

- GSK considers that the TGA may wish to consider modifying the time when a Sponsor has to lodge its application to extend a provisionally approved license from just before the expiry of the original 2-year period to when the Sponsor is required to lodge the next post-marketing Periodic Benefit Risk Evaluation Report (PBRER) for the provisional registration. In aligning the extension application timeline to the PBRER lodgement date, Sponsors will be less burdened in having to prepare a separate extension application which would be duplicative and burdensome on both Sponsors and the TGA.
- GSK also notes that it has experienced first-hand particular difficulties in obtaining an agreement with Clinical Research Organisations about the design and implementation of a Post Approval Safety Studies such as RMP commitments; and that this type of negotiation can take more time than expected. Consequently, GSK suggests that the TGA consider building in some flexibility for Sponsors as part the undertaking processes for the proposed provisional approval pathway to allow Sponsors to arrange any necessary post approval commitments.

Transitioning to full registration

Q14. Do you envisage any difficulties with the proposed process for transitioning a provisionally registered medicine to full registration?

GSK Comments

- GSK remains unclear as to why Sponsors will be expected to go through the formal, 12 to 14-month Category-1 registration process when transitioning from a provisional registration to a full registration. Given Sponsors will have presumably already submitted comprehensive quality, non-clinical and clinical data as part of their provisional approval application, a formal Category-1 registration process seems to be particularly long, given the intent is to provide not only medicine access but ongoing information to HCPs and patients.

Legislative and regulatory amendment

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

GSK Comments

- GSK notes that the TGA may be inundated with appeals from Sponsors should their provisional approval registration applications be rejected, similar to what occurred for the Business Reform Process (BRP) and the acceptance/rejection of applications on pre-submission. Therefore the ability for the TGA to impose strict criteria (to manage expectation), whilst leaving appropriate flexibility will be key. Furthermore, this

consultation document does not discuss whether the TGA has sufficient resourcing to deal with the possibility of an influx of appeals, and whether the influx of such appeals could delay other provisional approval applications. As a standalone point, this raises the consideration of TGA resources to manage the number of applications that may need to be reviewed against business as usual applications.

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?

GSK Comments

Reimbursement implications

- Based on experience with early promising clinical data, GSK considers that there will be considerable difficulty and complexity in providing subsidy to provisionally approved medicines through the Pharmaceutical Benefits Scheme (PBS).
- Industry is seeking clarity from the Government on how provisionally approved medicines will be assessed, should a subsidy application be put forward.
- Provisional approval may satisfy the Pharmaceutical Benefits Advisory Committee (PBAC) legislative requirements to make a recommendation for subsidy to Government; however, the PBAC is conservative in their approach to uncertainty resulting from incomplete or early data.
- It is anticipated that the PBAC would mandate a Managed Entry Scheme (MES) for subsidy of provisional approvals.
- A MES is a mechanism whereby the PBAC may recommend PBS coverage at a price justified by the existing or potential future evidence, pending submission of more conclusive evidence of cost-effectiveness to support the current or future price. It would appear that this avenue to date has not been utilised significantly by industry and therefore lacks predictability and confidence from a Sponsor perspective.

We thank the TGA for providing GSK with the opportunity to participate in this very important consultation process.

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