Medicines Australia

Scientific Operations Management
Scientific Evaluation Branch
Therapeutic Goods Administration
PO Box 100
WODEN ACT 2606
Email: generic.medicines.reform@tga.gov.au

Dear Sir/Madam

Re: Targeted Consultation on Reforms to the Generic Medicines Market Authorisation Process

Medicines Australia welcomes the opportunity to provide comment on the Therapeutic Goods Administration (TGA) targeted consultation for generic prescription medicines including the following guidance on use of overseas reference products; new international templates for bioequivalence studies and biowaiver justifications; and early advice on biowaivers:

- Section 15.6 of Guidance 15 Biopharmaceutic studies
- Bioequivalence Study Information Form
- BCS-based biowaiver template
- Additional strengths biowaiver template
- Guidance - Information for applicants completing the Bioequivalence Study Information Form
- Guidance - Information for applicants completing the biowaiver templates

Whilst the guidances have been released as part of the work relating to reforms of generic medicines marketing authorization processes, innovator companies currently include biowaivers and bioequivalence studies as part of their applications. The current requirements for Module 1.9 include completed Summary of bioavailability or Bioequivalence study forms or biowaivers if applicable. It is unclear if the intention is for the new templates for generic medicines to replace the current templates and Medicines Australia seeks clarification on this point.

Our submission has been prepared with the expert input of Medicines Australia's Regulatory Affairs Working Group (RAWG). Members are selected for their regulatory experience and industry knowledge and bring a whole-of-industry perspective to the consideration of regulatory issues that stand to impact to our sector. Our detailed feedback on the guidance is included in Attachment 1 Consultation feedback form which addresses the specific questions included in the consultation paper.

We appreciate being kept up to date on any further developments. Please contact Betsy Anderson-Smith (Policy Officer) on banderson-smith@medaus.com.au if you require further information.

Yours Sincerely,

Vicki Gardiner

Dr Vicki Gardiner
Director of Policy and Research
Medicines Australia

Australian Government
Department of Health
Therapeutic Goods Administration

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Attachment 1: Consultation feedback form

Feedback form for targeted consultation on
- use of overseas reference products
- new international templates
- early advice on biowaiver justifications

Section 1 General information

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Section 2 Consultation questions

Questions for use of overseas reference products in bioequivalence studies

1. Are the requirements in the revised guidance document presented in a manner that is clear and easy to understand?

The requirements are clear and scenarios are easily differentiated. It would be helpful to have the decision tree and evidence summary table together prior to the written scenario descriptions. The table makes it easy to visual the differences between evidence requirements across scenarios as reviewing the decision tree

2. Should there be a transition for implementation of the revised guidance document?
☒ Yes ☐ No ☐ Unsure

If yes, how long should this transition period be? 12-18 months

Questions for introduction of international templates

3. What further clarification is needed to make the questions in the templates easier to understand? You may provide your comment directly on the templates (see Attachments 3-5) and submit them with your feedback form.

The template questions are generally easy to follow with the support of the guidance document and the internal links to relevant CHMP technical guidance. The layout of the templates is clearer than the original IPRP template which facilitates completion.

Location of information based on volume is not relevant for eCTD submissions and should be marked as 'if applicable'.

The option to embed or attach relevant dossier sections or data files with the same information is important to avoid the very time consuming manual filling out of data tables .

It would be more practical if the question in the BCS-based biowaiver template as to whether the application relates to an NTI drug (Section 3.4) were at the beginning of the template. Answering yes to this question impacts the likelihood that a BCS waiver will be possible and consultation with TGA is advised. It therefore seems wasted effort to have initiated completion of the template if review of this question results in a decision not to proceed.

4. What additional clarification should be included in the guidance documents to make the process and evidence requirements easier to understand? You may provide your comment directly on these documents (see Attachments 6-7) and submit them with your feedback form.

The guidance document is generally clear in terms of the information expected to complete the different sections of the template. The information boxes in the guidance are also helpful.

5. Do you have any experience in using equivalent templates when making submissions to other regulatory agencies, for example, Health Canada or SwissMedic?
☐ Yes ☒ No

If yes, can you please provide the details?

6. Do you have any concerns with TGA mandating use of the templates and why?

The requirement to complete a template seems to originate due to an issue with locating all relevant information in the submission dossier. Completing templates has historically been required due to limitations in navigating paper submissions. It is a time consuming exercise which can easily introduce errors when data fields are populated.

The proposed templates are stated to apply to generic Rx medicines and it is unclear whether the same requirements will apply for innovator medicines who also complete bioequivalence studies or justify biowaivers. The existing Bio study forms are a lot simpler than the new templates which require substantially more details on study design and will take significantly longer to complete. Whilst for generic applications a single bio study may be sufficient, new molecular entity submissions may have multiple bio studies where changes in manufacturing processes, formulations and presentations have occurred. If the templates are planned for adoption for all Rx medicines the new template will have a substantial impact on time taken to prepare a complete Module 1.

The option to attach relevant data as a file will assist with completion, however creating lots of additional hyperlinks from the template to the location of data in the CTD adds complexity. The replacement of mandatory requirements ie no need for Module 2.5 provides an incentive for completing the templates for some generics and the option to utilise comparable overseas regulator templates is appropriate. For innovator companies submitting biowaivers or bioequivalence studies due to changes in product formulations or presentations either during development or as part of lifecycle management activities, the mandatory requirements will still apply and thus the templates represent additional work to be completed to finalise an application.

In the era of fully electronic submissions, creating an agreed internationally accepted harmonised structure for bio study reports and clearer guidance on where information must be located within the CTD would be an alternative and less burdensome way of ensuring all necessary data was available. This would fit within the remit of ICH activities that has broad overseas acceptance including the majority of parties represented on the IPRP and would represent a reduction in burden for Sponsors in creating additional documentation for Module 1.

7. Do you think a one (1) year transition is sufficient?
☒ Yes ☐ No ☐ Unsure

If no, how long should the transition period be? months

Questions for early advice on biowaiver justifications

8. Based on the information provided, can you give an estimate of the number of requests for early advice you might make per year?

Assuming the biowaiver justifications also apply to innovator Rx medicines, for global organisations, who represent the majority of Medicines Australia members, early development is often conducted overseas eg US or EU and Australia is more often included in later development phases. Biowaiver justifications will thereore most likely have been submitted to overseas regulators eg FDA and the potential uptake of TGA advice may be low.

9. Would any of the following aspects influence your decision to use the early advice process, and why?
    i) Data requirements to make a request for advice
    ii) Fee
    iii) Meaningfulness of advice
    iv) Timeframe

All of the factors would be considered when determining if seeking advice was worthwhile. Key considerations include assessment of the risk vs benefit of expending internal resources and funds to manage the early advice process with the likelihood of improved evaluation outcomes eg faster submission and approval or increased certainty of outcomesl

From the consultation paper it is not clear how 'full description' of proposed medicine is to be interpreted and what sufficient data means. The requirement to submit data in eCTD format implies complete M3 sections are expected whilst the evaluation time is estimated to be 1-2 days.The intent of early advice is to gain insights to support development planning which means information may not have been created in the final dossier format. This could be a deterent without clarity of expectations.

The inability for additional data to be requested as part of the advice process seems inflexible particularly as part of introducing a new process. This may be offputting as it would add to the risk of delay if a second submission were required.

It may be appropriate to consider a pilot program and utilise learnings to give Sponsors better clarity on expectations and create a more detailed guidance framework. This will avoid poor quality or excessive data being provided by Sponsors.

Fees should reflect cost recovery principles and the proposal to adjust submission fees if early advice sought should act as an incentive to obtain advice provided the outcomes are meaningful.

Meaningful advice must enable predictable outcomes during evaluation if advice is followed and allowances should be made where a development program followed advice aligned with available guidance at the time that subsequently changed at the point of of submission and prior to completion of an evaluation.

10. In the context of your submission development timelines, what would be an appropriate timeframe within which advice should be provided?

A rapid turnaround is important to ensure development plans can move forward as quickly as possible. The reference to evaluation time being anticipated to be between 1-2 days implies that the timeframes for receipt of advice should be possible within 2 weeks dependent on number of applications and background workload.

11. Do you have any comments on the proposed early advice process?

This is a positive initiative to increase the certainty on data requirements relating to biowaivers to avoid the conduct of unnecessary studies. The meaningfulness of advice and predictability of outcomes following evaluation if advice is followed will be key to the process being deemed successful.

12. If we were to expand the scope of the early advice process in the future, what other topics would you like us to include?

Thank you for completing the consultation feedback form for the targeted consultation. Please submit the completed form to Generic.Medicines.Reform@tga.gov.au by close of business on **26 September 2019.**