Medicines Australia – Response 9

CDx identification guide
"Inclusion of the CDx identification guide is very helpful for sponsors to determine whether CDx testing is required for the proposed medicine/biological with an accompanying need for in vitro testing. We provide the following comments related to Figure 1. CDx testing identification guide to assist in improving its clarity: a) Medicines Australia is of the view that the two boxes in the third line of Figure 1 could be merged into a single box. We believe that the box which asks the question “Is there confidence that use of standard of care local Australian testing in conjunction with the medicine/biological would result in comparable clinical outcomes to those seen in the clinical trial’ may be superfluous. It seems implicit that the response to the question in the preceding box which asks: “was the testing that was used to generate the pivotal clinical trial data consistent with mainstream pathology testing in Australia, such that standard-of-care local testing would be expected to result in comparable patient outcomes”, would take into consideration the matters for consideration listed in the subsequent box. b) The examples of mainstream pathology testing provided in Figure 1 represent traditional examples of tests that are not necessarily informative in the contemporary context of companion diagnostics. Could the examples listed here be expanded to cover established tests such as HER2, RAS, BRAF, EGFR? We note that case study 4 indicates TGA considers identification of HER-2 positive status in breast cancer to be well established in Australia. This example could therefore be included in Figure 1. c) The first footnote to the CDx identification guide on page 5 directs sponsors to contact the TGA, but it is unclear as to which Branch of TGA. Medicines Australia recommends that the footnote provide clear direction to contact the Prescription Medicines Authorisation Branch. d) Page 4 of the draft guidance indicates that the purpose of figure 1 is to help identify whether a proposed medicine or biological indication requires CDx testing. Further, page 10 of the draft guideline states that: “In lieu of a companion testing plan, Sponsors can submit a justification for why their proposed new indication does not require companion testing and that the TGA will consider the Sponsor’s justification and work with the Sponsor to determine whether the medicine requires companion testing. If a submission is identified where the TGA considers a proposed new medicine or biological indication does require companion testing, and a companion testing plan hasn’t been submitted, one will then be requested”. It would be helpful to clarify how and when this justification is to be submitted within the application process for the medicine/biological product. There is a concern that if the TGA disagrees with the conclusions of the medicine Sponsor that CDx testing is not required, this will emerge at the end of the evaluation of the application to register the Indication. This potentially will have a major impact on the Sponsor and the medicine/Indication. Agreement on this outcome should be reached prior to the submission or at an early point during the evaluation of an application to register an Indication which involves in-vitro diagnostic testing, to avoid unforeseen delays (also see comments under Companion Testing Plan)."
Companion testing plan
"Although the introduction of a Companion Testing Plan introduces a new regulatory requirement, Medicines Australia recognises the potential efficiency and clarity afforded by its implementation.

There are however a number of aspects which are causes of concern or require further clarification.

Suggested text revision:
In the opening paragraphs under the 'Companion testing plan' section heading, it appears that the guidance seeks to reassure medicine/biological sponsors that only a limited amount of information is required from them during the medicine registration process. In doing so, the guidance is not clear in the expectations of different possible scenarios. This could be clarified by including additional case studies or by including the scenario in the text where a Sponsor intends to utilise overseas testing for an interim period due to a delay in the availability of a planned Australian CDx (or notified in-house IVD test).

For example, the second paragraph under the 'Companion testing plan' section heading, could be replaced with "The Sponsor is required to describe how companion IVD testing will be made available to patients in Australia". The third paragraph remains the same, after which a paragraph is inserted which says "If the medicine sponsor intends to utilise overseas testing for an interim period due to a delay in the availability of a planned Australian CDx (or notified in-house IVD test) the sponsor should clarify this in the Companion testing plan."

Proposed alternative mechanisms for providing the TGA with data on the IVD that is not owned by the medicine/ biologic sponsor:
Furthermore, the guidance refers to the scenario where the IVD identified in the companion testing plan is a 'subsequent IVD' (ie a follow-on test to the clinical trial assay) and where there is no concurrent application for inclusion of a CDx in the ARTG or notification of an in-house CDx IVD. The guidance goes on to list the evidence the TGA wish to be provided. It may be challenging for medicine/biological sponsors to obtain the required performance and comparability data from the manufacturer of the IVD in order to include this data in the medicine/biological application, particularly in the situation where samples are being sent overseas for analysis. Reasons for this could include contractual issues, confidentiality concerns and logistical matters.
A mechanism where the manufacturer of the subsequent IVD provides the information directly to the TGA may be warranted to overcome these challenges. Moreover, in the scenario where testing of samples is proposed by the Sponsor to be undertaken overseas and the test is registered (or otherwise approved) by a Comparable Overseas Regulator, consideration should be given to accepting evidence of such registration/approval as satisfactory for TGA purposes rather than requiring the Australian medicine/biological Sponsor to provide the detailed evidence TGA require for a test conducted in Australia.

Suggest companion testing template be provided and clarification on process and timing of testing plan:
It would be helpful for TGA to identify a template for the companion testing plan and to describe the preferred location for its inclusion within the medicine/biological eCTD dossier structure.
Consistent with the comment above regarding the timing and timeliness of evaluation of justifications for there being no CDx testing requirements, timeliness of the evaluation of a Companion Testing Plan within the overall evaluation process will be very important. There is a concern that if the TGA disagrees with the proposals made by the Sponsor in the Companion Testing Plan, this could emerge at the end of the evaluation of the application to register the Indication. This could have a major impact on the Sponsor and the medicine/Indication. It would help if TGA clarified the process and timing aspects of this new requirement.

'Post-approval Actions' section may be unnecessary:
We suggest that inclusion of the heading "Post-approval Actions" is unnecessary as the information continues to be related to the general Companion Testing Plan concept.
We note that there may be a typographical error in the second paragraph of the Post-approval Actions section. It is presumed the first sentence of this paragraph should read "For indications

where no CDx is included in the ARTG (or notified as an in-house CDx IVD), as a condition of medicine or biological registration, the medicine or biological sponsor must notify the TGA if there are any substantial changes to the companion testing plan."

Flexible regulatory solution for managing ongoing compliance is critical:
The draft guidance proposes that post-approval changes to the companion testing plan will be managed through a type H application, and that this could include removal of a condition of registration. Based on industry's experience of Category 1 timelines the lead time for changes to the companion testing plan will therefore be 12-15 months. Given the rapidly evolving nature of precision medicine, a more flexible regulatory solution for managing ongoing compliance is critical to ensuring medicines access for patients."

Case studies

"The case studies provide useful information for stakeholders impacted by the draft guidance, and we encourage further use of case studies in this guidance to describe areas that would benefit from clarity. We note the opening sentence of this section states, "Below are four case study examples that may assist device sponsors in understanding clinical and analytical requirements when submitting a CDx application". However, case study 4 is related to the decisions of a medicine/biological sponsor. We suggest that this example be moved to a location related to the activities of medicine/ biological Sponsors or the introductory text to the case studies could be revised to clarify that the case studies assist both device and medicine sponsors in understanding the CDx regulatory framework.

Case Studies 2 and 3 are very similar. To further differentiate Case Study 3, it is recommended that the bridging study in this example should use specimens representative of those tested in the original pivotal clinical trials, as all the original clinical trial specimens are exhausted or inaccessible (real world). This could be achieved by revising the text of Case Study 3 as "The comparability studies included the specimens used in the pivotal clinical trials re-tested with 'NGS-Dx' to assess percentage agreement with the clinical trial assays or samples that are similar to those used in the pivotal clinical trials."

Additional scenarios that could benefit from case studies could include situations where onshore companion testing is infeasible; examples of when a proposed new indication does not require companion testing in lieu of a companion testing plan; and scenarios where a CDx IVD has a serious supply disruption. It would also be helpful to provide an example or examples of completed companion testing plans."

Further feedback

"The revised guidance adds valuable improvements and clarity to the current guidance. Since this guidance provides advice regarding both medicines/biologicals and devices to different stakeholders, it could be further refined by more clearly differentiating between these types of therapeutic goods.

Feedback re structure of the guidance:
Medicines Australia considers that the following sections or subsections are in fact guidance for sponsors of devices and should be relocated under the "What do device sponsors need to do?" heading:

- Use of a Unique Product Identifier (UPI) and separate applications for inclusion
- Applications for inclusion in the ARTG
- Mandatory application audit
- Abridged evaluations and overseas evidence
- Changes to CDx included in the ARTG

Numbering of the sections and subsections in the guidance could also provide greater clarity about the applicability of the guidance to different types of stakeholders.

Medicines Australia member companies request clarification on the following additional questions:

- Page 7 of the guidance states that “The new CDx regulations were introduced on 1 February 2020. Under the CDx regulatory framework, new applications for inclusion of an IVD CDx in the Australian Register for Therapeutic Goods (ARTG) will be subject to an amendment as per Regulation 1.6, and will require a UPI, which is unique to the CDx device and is given by the manufacturer of the device.“ - would the UPI assigned under IVDR be a suitable substitute to this?

- Page 7 of the guidance states that: “Applications for inclusion of a CDx in the ARTG will be subject to a mandatory application audit under subparagraph 5.3(1)(j)(x) of the Medical Device Regulations, unless supported by a conformity assessment document issued by a notified body under the European IVD Regulations (2017/746) or by the TGA.” - would FDA clearance or approval be a suitable substitute for this requirement?

- With the enforcement discretion policy phase-out under FDA’s Laboratory Developed Test Final Rule, it is expected that FDA will down-classify certain types of CDx from Class III (high risk, requiring full PMA application) to Class II (moderate risk, with 510(k) application). It will be helpful to know whether Australia (1) similarly intends to down-classify such devices and (2) would accept sponsor requests for abridgment of an application audit based on overseas evidence aligned with 510(k) [vs PMA] requirements

- Page 13: Scenario 3 of Figure 2 appears to suggest that all instances where a clinical trial assay is transferred to an Australian laboratory represent an in-house CDx IVD and will require notification to TGA as part of the annual notification process. We note the statement on page 18 that it is expected that NATA may request TGA’s assistance in the technical and clinical performance of an in-house CDx IVD due to the need to access proprietary information regarding clinical trial assay performance characteristics, and that TGA will undertake further consultation with NPAAC about whether there is a need to include additional information in the NPAAC Standard specific to validation of in-house CDx IVDs. Medicines Australia requests to be informed and involved about this consultation given the role of our member companies in submitting the proprietary information about clinical trial assay performance characteristics in establishing the medicine or biological Indication."