This response has been prepared by Roche, representing both our pharmaceutical (Roche Products Pty Ltd) and diagnostics (Roche Diagnostics Australia Pty Limited) divisions in Australia – Response 5

CDx identification guide
Roche is supportive of a CDx identification guide summarised in Figure 1, however Roche raises concerns below, and believes that clarity on these issues is required before implementation. In Figure 1, Roche would like clarity about the box which appears to apply a criterion on confidence about comparable patient outcomes (box in blue on lower, right side). Roche seeks clarification on the intent of including such a criterion. Roche assumes that if the testing is consistent with mainstream pathology testing in Australia then it would not be considered novel nor anticipated to have variability in performance. Based on this interpretation, Roche considers this box to be redundant. The examples of mainstream testing provided in Figure 1 represent traditional examples of tests (e.g. serum gentamicin levels) that are not necessarily informative in the contemporary context of companion diagnostics. It would be helpful guidance for sponsors if the guidelines were updated to include expanded examples to cover established tests such as HER2, PD-L1, BRAF, EGFR to assist in sponsor decision making in a modern context. Roche notes that case study 4 indicates TGA considers identification of HER2 positive status (IHC 3+/ISH+) in breast cancer to be well established in Australia. Roche suggests that this example could therefore be included in Figure 1 as well as other HER2 tests as part of the ongoing evolution of treatment of HER2 positive patients. Roche is concerned about a potential scenario where a Sponsor makes the determination that a new medicine (or new indication) does not require a CDx through following the CDx identification guide, but during the evaluation of the application the TGA disagrees and requests a CDx. In the current streamlined evaluation process the TGA Delegate does not provide an indication of their position on any issues with an application until late in the assessment process with the Delegate's Overview. In addition, in the scenario of a disagreement between TGA and the Sponsor on the need for a CDx, it is possible that the Delegate may ask the Advisory Committee on Medicines (ACM) to provide advice. This would mean that a final decision on the need for a CDx would come at the end of the assessment process. A final determination that is this late in the process would very likely lead to a delay in patient access to the new product or indication, as a CDx would subsequently need to be identified and/or developed. To avoid patient delays in this scenario, Roche suggests that the determination by the TGA on whether a product or new indication requires a CDx should be addressed early in the evaluation process or, preferably agreed upfront in the pre-submission phase.
Companion testing plan
Roche supports the inclusion of the companion testing plan as it acknowledges that it may not always be possible to submit an IVD CDx and a medicine concurrently. Furthermore, Roche welcomes the acknowledgement by the TGA that on-shore CDx testing may not always be possible or practical, and that the companion testing plan includes a mechanism for overseas CDx testing to be "approved" by TGA, where appropriate. However Roche raises some questions about the operation of the companion testing plan below, and believes that clarity on these issues is required before implementation. Firstly, the requirement for detailed information on the clinical trial assay (CTA) to be provided

upfront within the medicine's dossier creates an Australian-specific documentation requirement. Global medicine dossiers do not commonly include such information, even for a medicine that the Sponsor has determined to require a CDx.

Roche suggests that for global consistency this information should not be a requirement. However, if it is determined that it must be required, Roche recommends that the guidance is amended to account for scenarios where information on the CTA is not available at the time of submission of the medicine, so the requirement for this information does not delay the sponsor's ability to submit an application.

Furthermore, it is unclear in this guidance where in the Common Technical Document (CTD) the companion testing plan would be placed and therefore how the companion testing plan would be maintained. Roche suggests this document should be within Module 1, but there is currently no existing section where it logically would fit, and Roche suggests that the TGA provides guidance on this matter.

Additionally, it is currently unclear where in the CTD, information on the CTA or subsequent CDx would be placed. Roche suggests the guidance includes suggestions for appropriate placement of this information in the CTD.

Finally, the draft guidance says the Type H application category be used for changes to the companion testing plan requiring data evaluation. Type H applications have an evaluation timeframe of approximately one year under the streamlined submission process. Roche suggests due to the lengthy time frame of these applications, it would be ideal for the TGA to consider a notification-style pathway, such as that used for changes to Risk Management Plans.

Recognition that some CDx may need to be conducted overseas
Roche welcomes the recognition within the guidance that it may not be possible or practical for CDx testing to take place in Australia for every medicine or biological that requires a CDx.

The guidance includes the following statement:

"Sending of samples to an appropriately accredited overseas testing facility is considered acceptable by the TGA only if development of onshore testing with an ARTG-included or in-house (notified) CDx test is infeasible or incomplete."

Roche supports this regulatory flexibility, but also encourages the TGA to expand on the circumstances of where development may be "infeasible" by including situations or examples where this may apply. For example, CDx testing of patients with orphan diseases where centralised testing in a limited number of global centres is more practical and efficient.

Due to the low prevalence of these diseases, there are issues with testing throughput which can affect the turnaround time and extend the time to diagnosis/test results, which potentially delays effective treatments affecting patient outcomes. In this scenario Roche considers that overseas testing would likely be the permanent and pragmatic solution for the life of the registered medicine.

While acknowledging the potential time lost due to transport for overseas testing, there are likely to be greater efficiencies at the point of testing which would result in improved timeframes overall for orphan diseases. This efficiency is driven by a higher number of samples and more frequent running of the assays at a centralised laboratory.

Case studies

The inclusion of case studies is a welcomed practical guide for reference examples.

Further feedback
Roche is also supportive of the Medicines Australia response to the consultation and many of the points raised are consistent with that submission. Roche has the following additional comments on the draft guidance. Flow on effects for reimbursement processes Roche believes that the guidance document has potential flow-on consequences for co-dependent reimbursement pathways. Roche understands that the TGA has consulted with the Technology Assessment and Access Division (TAAD) within the Department of Health and Aged Care (DoHAC) to fully consider any impact on TAAD processes, and Roche suggests that the guidance be updated to include relevant information about reimbursement considerations. To ensure there are no unintended consequences to effectively and efficiently enable parallel subsidised access for the Australian community, Roche believes that in the interest of transparency, it would be ideal to provide TAAD feedback publicly. Sponsors could consequently provide further consultation comment, if required. Product Information wording for CDx Roche supports the proposed Product Information (PI) wording in the draft guidance and the proposal that it should be placed in section 4.4 of the PI (Special warnings and precautions for use) as a subheading. Roche believes that this is the most appropriate place for this wording as it is an important precaution considering the CDx is needed for the safe and effective use of a medicine. Minor comments Finally, Roche would like to make a minor suggested change to Page 4 in regard to biological PI and Instructions For Use (IFU). This section states: “As the wording of the medicine or biological PI and the IFU are determined during the medicine registration process…” Roche suggests that the wording of the IFU would not be determined during the medicine process as the IFU is specific to the device (IVD CDx).