AusBiotech submission regarding proposed performance requirements and risk mitigation strategies for HIV tests

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Introduction

AusBiotech is pleased to submit to this consultation regarding the TGA's proposed performance requirements and risk mitigation strategies for HIV tests, based on comments and submissions from AusBiotech members and from many years of working to grow Australia's strength in biotechnology.

AusBiotech is a well-connected network of over 3,000 members in the life sciences industry, which includes medical technology (devices and diagnostics), bio-therapeutics, food technology, industrial and agricultural biotechnology sectors. The industry consists of an estimated 900 biotechnology companies (400 therapeutics and diagnostics and 500 – 900 medical technology companies) and employs in excess of 45,000 Australians.

The rapidly changing developments in the sensitivity and ease of use of diagnostic devices has led to the opportunity to improve access to testing and the potential to improve the detection of HIV and other communicable diseases. In this environment AusBiotech supports the TGA's efforts to periodically review performance expectations and risk mitigation strategies for these devices. Advances in the performance of in-vitro diagnostic (IVD) technologies means that the assumption that testing at point-of-care (PoC), or the self-testing environment, is less sensitive than laboratory-based testing, may be less applicable than it has been in the past.

AusBiotech cautions the TGA to consider the regulatory burden impacts of testing requirements proposed for HIV self-test devices. For example, AusBiotech members have suggested that the proposal for HIV self-tests to have the same performance requirements as those specified for HIV point-of-care test (PoCT) when used in a controlled laboratory environment will unnecessarily require self-test IVD manufacturers to conduct studies at PoCT sites or under controlled laboratory conditions in addition to the intended-use environment. It would be preferred that the TGA specify acceptable levels of sensitivity and specificity as has been provided for the other intended uses.

AusBiotech applauds the TGA consideration of the performance expectations of tests in overseas jurisdictions and urges the Administration to continue to seek harmonisation of performance requirements and risk mitigation strategies for diagnostic and medical devices.

Comments on the proposed performance requirements:

A. General comments

- Whilst it is the case that HIV testing performed at point-of-care or in a self-testing environment has generally been considered less sensitive than laboratory-based testing, it must be noted that this is rapidly changing with the development and introduction of new technologies.
- AusBiotech welcomes the TGA's efforts to seek harmonisation with overseas jurisdictions' requirements.
- The scope of the paper specifically excludes performance requirements for HIV nucleic acid tests. The rationale for this is not clear. The minimum performance requirements (sensitivity, specificity, usability, robustness, etc.) should be the same for all products and not dependent on the technology used to achieve the specifications. AusBiotech recommends that all technologies are included.

- AusBiotech strongly agrees with the statement that HIV self-testing will improve access to testing and result in increased rate of testing, which in turn has the potential to improve the detection of HIV, facilitate earlier access to treatment and reduce transmission rates. AusBiotech encourages the TGA to extend this rationale to other self-tests and for them to be made available to the Australian public for the same reasons.
- Regarding the following statement: 'It is then recognised that the same level of performance may not be achieved in a self-testing environment,' AusBiotech members suggest that in a well-designed self-test IVD, which has taken into consideration the intended use population (lay-user) and incorporated appropriate human factors design inputs, the same level of performance should be expected.
- AusBiotech members would prefer that the TGA state what the acceptable performance standard for HIV tests should be no matter what the intended user population and environment. It should be the same for self-testing and for PoC testing. Notwithstanding, if the TGA expects and is willing to accept lower performance standard for self-tests then they should be more specific than just stating that performance must be 'adequate'.
- Throughout the document the TGA discusses that the suitability of studies will be assessed on a case-by-case basis and would depend on how well the manufacturer has mitigated any risks and demonstrated that overall benefits of the product outweigh any residual risks. Guidance on what the TGA expects a manufacturer to present with regard to benefits/risks within a submission would be extremely helpful. For example, AusBiotech believes that the scope of the risk/benefit assessment should be limited to risks and benefits to the individual self-tester and immediate contacts rather than assessing the risks to the broader community and economy. Being clear about what is expected provides clarity in scope of investment required by a manufacturer developing a potential self-test IVD. Economic modelling can be a significant cost and early planning is required.

B. Laboratory testing

- The proposed sensitivity and specificity performance requirements presented in Table 1 appear appropriate.
- AusBiotech members suggest that it would be helpful if the sensitivity and specificity were expressed with the confidence intervals that the TGA is expecting so that manufacturers are prepared to design appropriately powered performance evaluations.

C. HIV PoCT

- The proposed sensitivity and specificity performance requirements appear appropriate, however, as for laboratory testing, it is recommended that requirements for sensitivity and specificity are expressed with acceptable confidence intervals.
- It is unclear why sample types have been limited to whole blood and oral fluid. Whilst the current tests available may be limited to these sample types, tests are developed and available in other regulatory jurisdictions that have been validated for use with serum and plasma. AusBiotech recommends including all sample types (it is noted that no sample type is specified for laboratory tests).

D. HIV self-tests

It would be helpful if the TGA could clearly define the following parameters relating to HIV self-tests:

- Acceptable levels of sensitivity and specificity. The proposal for HIV self-tests to have the same performance requirements as those specified for HIV PoCT when used in a controlled laboratory environment will unnecessarily require self-test IVD manufacturers to conduct studies at PoCT sites or under controlled laboratory conditions in addition to the intended use environment (self-testing). It would be preferred that the TGA specify acceptable levels of sensitivity and specificity as has been provided for the other intended uses.
- It would be helpful to manufacturers for the TGA to clearly define 'effective' when stating 'effective sensitivity'. It is understood this depends on the risks v benefits, however, the same could be said for PoCT where quite specific acceptable sensitivity and specificity has been defined.
- A clear statement defining acceptable limits for 'low inter-reader variability' would be very helpful and would enable manufacturers to set minimal acceptable performance requirements. In this way specific design input targets can be included from the start of the development process rather than potentially have to redesign the product at a later date.
- AusBiotech cannot comment on the validity or otherwise of an invalid/error rate of <2%. It may be appropriate; however, as no rationale has been provided, it is difficult to comment.

Comment on mitigation strategies, including conditions:

A. Laboratory testing

- The risk mitigation strategies described in the proposal appear to be appropriate.

B. HIV PoCT

- AusBiotech members agree in principle with making available training in correct use of the device as a mitigation strategy. However, members were unclear whether the proposal implies that the sole responsibility for training lies with the manufacturer. This would be unlikely to be acceptable to manufacturers and may result in undermining the TGA's efforts to open up access to these devices. As professional users, the onus should also be on the users to train their staff on the correct use of the IVD. This is no different to any other medical device/health-related equipment used in PoC environments where training is a shared responsibility. The design of Instructions for Use (IFU) and accompanying collateral by the manufacturer would be elements of 'labelling' that the TGA reviews through the standard review process.
- AusBiotech shares the concern that unnecessarily burdensome conditions placed on PoCTs may adversely impact the uptake of PoC testing. The proposed requirement to provide TGA with regular reports on the distribution of the product and numbers of any false positive or false negative results or problems with the test is considered unnecessarily burdensome for both manufacturers and the TGA. It does not represent a harmonised approach.

A manufacturer's ISO 13485 certified QMS already requires that all reported customer complaints (including reported false positives and false negatives) be captured and analysed for trends, and for corrective action to be taken. These reports include recall of product (and therefore TGA notification) when product is not meeting claimed performance specifications and also includes the reporting of any adverse events. AusBiotech suggests that the additional burden of regular reporting (when there is no problem with the product) will have no additional benefits to existing safeguards and may act to retard the TGA's aim to open up access to such devices, and therefore on balance is not in the best interests of the TGA or the community.

C. HIV self-tests

- Generally it is agreed that all of the proposed mitigation strategies presented would be appropriate, however, AusBiotech would like to caution against being too prescriptive in the way in which certain risks should be addressed.

  A specific example is in the requirement to provide instructions in multiple languages. The risk of incorrect interpretation of instructions and subsequent test results may be addressed in other ways. For example, this could be done through thoughtful design features incorporating elements that make the IVD intuitive to use (acknowledging that many people do not read instructions) and by designing an IFU with pictograms and well known accepted symbols.
- AusBiotech members do not agree with proposed conditions of supply, for the same reasons stated for PoCT conditions of supply.
- The condition that the TGA states may be applied regarding sponsor providing additional support for users of the test through provision of an on-line service and/or a 24 hour phone line is appropriate, however clarification is sought on the following:
    - If this refers to support on how to collect a sample, perform and interpret the test, then this is a reasonable condition;
    - If this refers to support in the form of pre- and post-test counselling then this would be an unreasonable and inappropriate condition. It would be a significant investment for the sponsor and would likely be a disincentive to supply.