Response to Consultation: Proposed performance requirements for tests to detect the presence of human immunodeficiency virus (HIV).

Submitting organisation: NRL

Thank you for the opportunity to comment on these proposed performance requirements.

Comments on performance requirements

NRL agrees with the performance requirements for devices in different settings as shown in Table 1. If all PoCT and Self-tests that were to be included on the ARTG met these criteria, we could be confident that only high quality devices would be in use. However, we do not believe that only devices meeting these performance requirements will be included on the ARTG.

Comment on risk mitigation strategies and TGA conditions

The risk mitigation strategies as proposed are valid examples. However, while the document uses "must" in many of its strategies, we are not convinced that if the criteria set out in a strategy were not met that the device would be rejected for inclusion on the ARTG. The tone of the whole document is flexibility, case-by-case analysis, consideration of all the contributing elements to a device's registration. While flexibility is positive, in its present form it will not result in consistent decision making. Much of the document seems to lay the groundwork for decisions to be made case-by-case; that the proposed performance criteria are desirable, but not necessary to be enforced. Decisions will be made subjectively, in consideration of evidence, availability of alternatives, possibly community pressure. With this approach decisions cannot be consistent time to time.

In our opinion, the guidance to be developed needs to be fairly prescriptive to ensure that devices can be assessed consistently from one to the next. In the present document, the risk mitigation strategies seem to imply that considerable flexibility would be afforded depending on the extent and quality of the dossier information and instructions for use. Without clear guidance, decisions made by different assessors and / or delegates will be subjective and by their very nature inconsistent with each other. In our opinion, flexibility without clear guidance and defined thresholds that lead to action will lead to inconsistency in the quality of devices available.

We agree with the imposition of considered and clear TGA conditions on devices, developed in consultation with stakeholders where necessary.

Specific Comments; Laboratory Tests

- [redacted]

[redacted]

- The reference provided for the EU-CTC is:
  "Commission Decision 2002/364/EC of 7 May 2002 on common technical specifications for in vitro-diagnostic medical devices."
  However, it should be noted that there is later a version (which NRL uses):
  "COMMISSION DECISION, of 27 November 2009, amending Decision 2002/364/EC on common technical specifications for in vitro diagnostic medical devices (notified under document C(2009) 9464), (Text with EEA relevance), (2009/886/EC)"
- It is not valid to express seroconversion sensitivity as it has been in Table 1. The concept of seroconversion sensitivity as described in the document (Section 2.1 Laboratory Tests) is flawed. To expect 100% agreement in seroconversion samples with equivalent devices is not valid e.g. a seroconverting sample with reactivity close to the cutoff of an assay may be reactive in one run or lot number of the assay, but negative in the next. This variation does not imply poor performance. It also makes it invalid to rank the performance of another assay based on detection or otherwise of seroconverting samples. Seroconversion sensitivity is necessarily conducted using small sample sizes (each panel represents several bleeds from an individual). It would be difficult to conclude that a device was unsuitable based solely on analysis of its seroconversion performance. NRL adopts the approach used my many manufacturers that for seroconversion sensitivity the overall performance of a device be comparable to that of the similar devices. Only if a device could be observed to have demonstrably and substantially worse seroconversion sensitivity than comparable devices would this be a cause for concern.

- The proposal is confusing in that appears to state that laboratory-based tests will continue to be held to the high standard (i.e. 100% sensitivity) stipulated in the EU-CTS, but that for "laboratory-based rapid tests intended for screening of confirmatory diagnosis, the performance requirements would be the same as for HIV PoCT described below". That is, laboratory-based rapid tests would be held to a lower standard than other devices used in a laboratory (e.g. ELISA, etc).

  Allowing rapid tests that have diagnostic sensitivity < 100% to be used in a laboratory setting for screening or confirmatory diagnosis will serve only to lower the quality of laboratory testing or at least confound the results.
  This particular detail of the proposal should not be adopted - The proposal should be modified to:
  "For laboratory-based rapid tests intended for screening of confirmatory diagnosis, the performance requirements would be the same as for ~~HIV PoCT described below~~ other laboratory tests described below Table 1"

- NRL supports the decision to continue to be guided by the EU-CTS for laboratory-based tests (including rapid tests). The EU-CTS provides useful guidance on the numbers and types of specimens that should be tested in order to ensure that a device performs according to its intended use. However, the EU-CTS requires testing with in comparison with a state-of-the-art "predicate" test. NRL does not support this approach. NRL recommends the use of a validated testing algorithm to determine the true HIV status of a specimen prior to evaluating the performance of a device.
  Determination of a specimen's "true" status prior to testing decreases the risk of ad hoc, selective winnowing of inconvenient/embarrassing results. Therefore the EU-CTS should continue to be used to provide guidance for sample sizes (e.g. 400 HIV-1 specimens, etc),

acceptance criteria (all true positive samples shall be identified as positive") and the like; however, we consider the requirement that this necessarily and specifically be done in comparison with a state-of-the-art device is not the best approach.

Specific Comments: HIV Point of Care Tests

- In the section "Risks", the risk of false positive results is not included. Its absence indicates that the requirement for confirmation of reactive results is considered all that is necessary to mitigate the risk of false positive results. We believe that the guidance would benefit from specific consideration of the risks imposed by false positive results. With specific consideration, there may be other mitigating measures besides the requirement for confirmation.
- One of the purposes of the consultation is to comment on proposed conditions that TGA might impose,. The document points out conditions that could be placed on HIV PoCT and that the imposition of the conditions "would ensure that high quality tests are used at the point-of-care…". Yet the next paragraph seems to cast doubt on the usefulness of TGA conditions and comments that conditions placed on the currently registered HIV PoCT are considered restrictive by some stakeholders. NRL believes that conditions play a useful role in ensuring the quality of testing and that they could be more acceptable if developed in consultation with stakeholders.

Specific Comments: HIV Self-tests

- It should be noted that the EU-CTS requires devices for self-testing meet the same requirements as devices for laboratory testing (i.e. 100% sensitivity, >99.5% specificity).
- It is stated in the proposal that:

  "the IFU must clearly state the limitations of the procedure, that:
  - *negative results obtained within three months of a high risk event should be repeated at three months to confirm the initial negative result (i.e. false negative results can be obtained if testing is performed during the 'window period')*
  - *positive results require confirmation using another test method; and*
  - *all results should be evaluated in light of the overall clinical evaluation before a diagnosis is made"*

  It should also be a requirement that it is clearly stated (i.e. over and above simply stating diagnostic sensitivity and specificity, which a lay-user should not be expected to understand the implications of) that a result of negative after 3-month retesting does not guarantee absence of HIV antibodies for a device with <100% sensitivity.
- NRL recommends that devices intended for use in PoCT and/or self-test settings have precision (e.g., as a minimum, inter-reader variability) determined using a consumer field trial where untrained users operate the device using ***only*** information provided in the device's Instructions for Use. This is consistent with the requirement set out in table 1 for Effective Sensitivity studies to be included in dossiers of self tests
- In the proposal, for self-test devices, it is stated that:

  "information on behaviour that may place an individual at an increased risk for HIV infection, including a warning that a negative result does not indicate that engaging in high risk behaviour is safe"

  this seems a reasonable risk mitigation strategy (if it must be accepted that lower standards of quality/performance will be adopted).