Technical Specifications Series
for submission to WHO Prequalification –
Diagnostic Assessment

TSS-3  Malaria rapid diagnostic tests
TechnicalSpecificationsSeriesforsubmissiontOWOPrequalification–DiagnosticAssessment
Malariardapiddiagnostictests
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List of contributors
The draft technical specifications document was posted on the WHO website for public consultation on 05 December 2017. Various stakeholders, including manufacturers submitting to WHO Prequalification of IVDs, IVD manufacturing industry associations, various national and international regulatory bodies, and IVD standards organizations were informed of the consultation in order to solicit feedback. A two month response period was provided.

Public comments were received from the following: Shanghai Kehua Bio-engineering Co., Ltd, Shanghai, China; Standard Diagnostics, Inc, Gyeonggi-do, Korea.
## Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>ANOVA</td>
<td>analysis of variance</td>
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<tr>
<td>HAMA</td>
<td>human anti-mouse antibody</td>
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<td>IgG, IgM</td>
<td>immunoglobulin G and M</td>
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<tr>
<td>IVD</td>
<td>in vitro diagnostic medical device</td>
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<td>PCR</td>
<td>polymerase chain reaction</td>
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<tr>
<td>pfHRP2</td>
<td><em>Plasmodium falciparum</em> Histidine-Rich Protein 2</td>
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<td>pLDH</td>
<td>plasmodium lactate dehydrogenase</td>
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<tr>
<td>RDTs</td>
<td>rapid diagnostic tests</td>
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<td>WHO</td>
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A. Introduction

The purpose of this document is to provide technical guidance to in vitro diagnostic medical device (IVD) manufacturers that intend to seek WHO prequalification of IVDs for the detection, in blood, of antigens produced by *Plasmodium* (malaria) species. For the purposes of WHO prequalification, this document applies to only to rapid diagnostic tests (RDTs) intended to diagnose malaria infection.

For the purpose of this document, the verbal forms used follow the usage described below:

- “shall” indicates that the manufacturer is required to comply with the technical specifications.
- “should” indicates that the manufacturer is recommended to comply with the technical specifications but it is not a requirement.
- “may” indicates that the technical specifications are a suggested method to undertake the testing but it is not a requirement.

A documented justification and rationale shall be provided by the manufacturer when the WHO prequalification submission does not comply with the required technical specifications outlined in this document.

Minimum performance requirements for WHO prequalification are summarized in this document and, where possible, are aligned with published guidance, standards and/or regulatory documents. Although references to source documents are provided, in some cases WHO prequalification has additional requirements. External quality controls are outside the scope of this document.

For WHO prequalification purposes, manufacturers shall provide evidence in support of the clinical performance of an IVD to demonstrate that reasonable steps have been taken to ensure that a properly manufactured IVD, being correctly operated in the hands of the intended user, will detect the target analyte and fulfil its indications for use.

WHO prequalification requirements summarized in this document do not extend to the demonstration of clinical utility, i.e. the effectiveness and/or benefits of an IVD, relative to and/or in combination with other measures, as a tool to inform clinical intervention in a given population or healthcare setting. To demonstrate clinical utility, a separate set of studies is required. Clinical utility studies usually inform programmatic strategy and are thus the responsibility of programme managers, ministries of health and other related bodies in individual WHO Member States. Such studies do not fall under the scope of WHO prequalification.

B. Other guidance documents

This document should be read in conjunction with other WHO guidance documentation, including:

- Technical Guidance Series for WHO Prequalification – Diagnostic Assessment
- Sample Product Dossiers for WHO Prequalification – Diagnostic Assessment
- Instructions for Compilation of a Product Dossier, WHO document PQDx_018.

These documents are available at: [http://www.who.int/diagnostics_laboratory/evaluations/en/]
C. Performance Principles for WHO Prequalification

C.1 Intended use
An IVD intended for WHO prequalification shall be accompanied by a sufficiently detailed intended use statement. This should allow an understanding of at least the following:

- The function of the IVD (e.g. to detect *P. falciparum* infection; pan-specific detection of all *Plasmodium* species; detection of, and differentiation between, *Plasmodium* and non-*Plasmodium* species);
- The testing population for which the functions are intended (e.g. paediatric testing, symptomatic patients); and
- Clinical indication (e.g. to diagnose malaria infection).

C.2 Diversity of specimen types, users and testing environments and impact on required studies
For WHO prequalification submission, clinical performance studies should be conducted using the specimen types most likely to be used in resource-limited WHO Member States (i.e. capillary whole blood) and are claimed in the instructions for use. If this is not possible, data should be presented to show the equivalence between specimen types used in performance studies.

Prequalified IVDs in low- and middle-income countries are likely to be used by laboratory professionals\(^1\) and at point-of-care by healthcare workers or trained lay providers\(^2\). Depending on the intended use of a RDT, performance studies shall be designed to take into account not only the diversity of knowledge and skills across the population of RDT users, but also the likely operational settings in which testing will occur. For example, studies that comprise the testing of left-over/repository specimens by research and development staff at a manufacturer’s facility would, on their own, be considered insufficient to meet many of the performance requirements summarized in this document.

Malaria testing often occurs in conditions of high temperature (>35 °C) and humidity. It is a manufacturer’s responsibility to ensure that the risk assessment for an IVD reflects the intended operational settings and testing population.

C.3 Applicability of supporting evidence to IVD under review
The true *Plasmodium* status of a specimen shall be determined using a suitable reference method, for which justification shall be provided.

Estimation (and reporting) of IVD performance shall include the rate of invalid test results (where ‘invalid’ is a result interpretation defined in the instructions for use).

Analytical studies should be undertaken with natural specimens. Contrived specimens (e.g. where normal human specimens have been spiked with *Plasmodium* reactive specimens) should only be

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\(^1\) Medical technologists, medical laboratory technicians or similar, who have received a formal professional or paraprofessional certificate or tertiary education degree.

\(^2\) Any person who performs functions related to healthcare delivery and has been trained to deliver specific services but has received no formal professional or paraprofessional certification or tertiary education degree.
used in the submitted studies if a justification is provided. The use of recombinant *Plasmodium* antigens should be avoided. Clinical studies should be based on testing in natural specimens only.

Performance studies shall be undertaken using the specific final, locked-down version IVD intended to be submitted for WHO prequalification. Where this is not possible (e.g. because of design variation), a justification for use of earlier versions of the IVD shall be provided; additional supporting evidence may also be required. This may occur following minor variations to design where no negative impact on performance has been demonstrated.

For IVDs that include a claim for detection of multiple antigens and/or species, evidence of performance shall be provided for each claimed antigen and/or species. IVDs claiming to provide ‘pan’-specific detection of malaria are expected to detect all known pathogenic species of *Plasmodium*, i.e.: *Plasmodium falciparum*, *P. vivax*, *P. ovale*, *P. malariae* and *P. knowlesi*. Where a claim is made for ‘pan-specific’ detection of *Plasmodium* species, performance characteristics shall be determined in each species for which specimens are available. At a minimum this shall include detection in specimens positive for *P. falciparum* and *P. vivax* (Note that that for WHO prequalification purposes, studies incorporating specimens characterised as ‘non-*P. falciparum*’ will not be considered acceptable. Full characterisation of species is required and reporting should clearly state results for each species. If performance characteristics are not established for all relevant species of *Plasmodium* in IVDs claiming detection of “pan”-specific detection, this limitation of the IVD shall be clearly reported as a warning to the user in the instructions for use.

It is important to note that, depending on the design of an IVD, evidence generated in a similar, related product will not be sufficient to support performance claims in an IVD submitted for WHO prequalification. For example, evidence of *Plasmodium falciparum* Histidine-rich protein 2 (PfHRP2) detection in a PfHRP2-only IVD will not be accepted as evidence to support PfHRP2 detection in a subsequent dual-detection version of the IVD designed to detect both PfHRP2 and *Plasmodium* lactate dehydrogenase (pLDH).
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# Technical Specifications for WHO Prequalification of malaria RDTs

## TSS-3

### Part 1 Establishing analytical performance characteristics

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<td>1.1.1 Demonstration of equivalence between specimen types</td>
<td>For each claimed specimen type, testing in at least:  - 25 <em>Plasmodium</em> negative specimens  - 25 <em>Plasmodium</em> positive specimens.  Equivalence shall be determined for each claimed <em>Plasmodium</em> antigen and/or species, as appropriate.</td>
<td>1. The relationship between IVD performance in claimed specimen types and reference materials used for analytical studies shall be clearly established. The design of subsequent studies shall then take that relationship into account.  2. If there is no equivalence between claimed specimen types then the impact that this will have on each subsequent performance claim shall be fully understood and described. <em>Example: an IVD intended for testing whole blood for which the measuring range is estimated using panels of serum/plasma specimens.</em>  - The relationship between analytical sensitivity in serum/plasma to that of the same characteristic in whole blood shall be understood.  - <em>This may be achieved by comparing end-point dilution series of matched positive patient specimens (whole blood vs. serum/plasma collected from the same patient at the same time for testing) or may be determined as part of clinical studies.</em>  3. Positive specimens shall be chosen so that a majority are near the cut-off.</td>
<td>Technical Guidance Series for WHO Prequalification – Diagnostic Assessment <em>(1)</em></td>
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<td>1.1.2 Demonstration of equivalence of claimed anticoagulants</td>
<td>For each claimed anticoagulant, testing in at least:  - 25 <em>Plasmodium</em> negative specimens  - 25 <em>Plasmodium</em> positive specimens.  Equivalence shall be determined for each claimed <em>Plasmodium</em> antigen.</td>
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<td><strong>1.2 Specimen collection, storage and transport</strong></td>
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<tr>
<td>1.2.1 Specimen stability</td>
<td>Real time studies taking into account:  - storage conditions (duration at different temperatures and variation in humidity, temperature limits, freeze/thaw cycles)  - transport conditions, where applicable  - intended use (see comment 1)  - specimen collection and/or transfer devices,</td>
<td>1. Particular attention shall be paid to the length of time likely to elapse between specimen collection and its addition to the IVD in the settings where this IVD may be used.</td>
<td>Technical Guidance Series for WHO Prequalification – Diagnostic Assessment <em>(2)</em></td>
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### Technical Specifications for WHO Prequalification of malaria RDTs

**Aspect** | **Testing requirements** | **Notes on testing requirements** | **Source documents**
--- | --- | --- | ---
| | whether these contain anticoagulants and whether they can be sealed. |  | CLSI EP05-A3 (3) CI EP17 (4) EN 13612:2002 (5) |

### 1.3 Precision of measurement

#### 1.3.1 Repeatability, reproducibility

Both repeatability (within-condition – see comment 1) and reproducibility (between-condition – see comment 1) shall be estimated by replicate testing of end-point dilutions of several analyte-positive specimens. Specimens chosen for the testing panel shall include panel members that reflect the main specimen types intended for use with the IVD (e.g. capillary or venous whole blood).

Each panel member shall be tested:
- using 3 different lots (see Comment 9)
- over 5 days (not necessarily consecutive) with one run per day (alternating morning/afternoon)
- at each of 3 different testing sites

The effect of operator-to-operator variation on IVD performance is to be included as part of the precision studies (see also Comment 10). Testing should be performed:
- by personnel representative of intended users
- unassisted
- using only those materials provided with the IVD (e.g. instructions for use, labels and other instructional materials).

1. E.g. within- or between-run, -lot, -day, -operator, -site, etc.
2. Precision shall be determined for each analyte for which detection is claimed (e.g. PfHRP2, pLDH, etc., as appropriate).
3. Where possible, the testing panel should be the same for all operators, lots and sites.
4. Low-reactivity specimens shall be chosen that are sufficiently close to the assay cut-off to allow changes in IVD sensitivity to be detected.
5. The numbers of invalid tests shall be reported.
6. Lots shall be composed of different batches of critical components.
7. Results shall be statistically analyzed using analysis of variance (ANOVA) techniques to identify and isolate the sources and extent of any variance.
8. In addition to ANOVA, the percentage of correctly-identified, incorrectly-identified and invalid results shall be tabulated for each specimen and be separately stratified according to each of site, lot, etc. This type of analysis is especially important for rapid tests that may not have any numerical values for ANOVA analysis.
9. To understand irregularities in results obtained, at least 2 lots should be tested at each of the 3 testing sites.
10. The effect of operator-to-operator variation on IVD performance may also be considered as a human factor when designing robustness (flex) studies (see 1.10.1 Flex studies). The results of estimating operator-to-operator variation on IVD performance may be used in conjunction with studies to qualify the usability of the IVD.
11. Users shall be selected based on a pre-determined and
## Aspect Testing requirements Notes on testing requirements Source documents

### 1.4 Performance panels

#### 1.4.1 Performance panels

Testing of the IVD shall be against suitable performance panels (e.g. comprising relevant antigen variants, subtypes, etc.) where these are available.

Specimens that are *Plasmodium*-positive shall be correctly identified by the IVD.

1. Testing should be performed using more than one lot of the final design (locked-down).

WHO Prequalification – Diagnostic Assessment (6)

### 1.5 Validation of reading time

#### 1.5.1 Validation of reading time

For IVDs where a reading interval is specified (i.e. time when result can first be read; time beyond which result should not be read), validation of critical time points shall be provided. Performance studies shall be conducted at the intended operational temperature range; the effect of humidity on reading times shall also be investigated.

1. The ranges of temperature and humidity tested for should be risk-based, taking into consideration knowledge of conditions likely to be experienced in intended operational settings.

2. The intended operating temperature, upon which reading time has been validated, shall be clearly stated in the instructions for use.

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<td><strong>1.6 Analytical sensitivity</strong></td>
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<td></td>
<td></td>
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<tr>
<td><strong>1.6.1 Analytical Sensitivity</strong></td>
<td>Analytical sensitivity shall be determined for each claimed antigen (e.g. PfHRP2, pLDH, etc.) and/or species, as appropriate. The determination of analytical sensitivity may comprise a minimum of 15-20 replicate tests of an 8-member dilution panel of a suitable biological material. Analytical sensitivity shall be estimated by determining the lowest concentration for which the rate of detection is 95%.</td>
<td>1. Analytical sensitivity shall be sufficient to allow detection of a minimal clinically significant antigenemia, consistent with the median concentration of target antigen in the WHO Malaria rapid diagnostic test performance evaluation programme. 2. Justification shall be provided for the choice of reference material used to determine the concentration of target antigen. 3. Optimally, testing should be conducted using more than 1 lot of the final locked-down design. 4. Analytical sensitivity should be demonstrated in a clinical sample matrix and should use the entire assay system from sample preparation to interpretation. 5. The estimate of analytical sensitivity should be confirmed by separately testing an additional 20 replicates. 6. Where a claim is made for ‘pan-specific’ detection of Plasmodium species, performance characteristics shall be determined in each species for which specimens are available. At a minimum this shall include detection in specimens positive for \textit{P. falciparum} and \textit{P. vivax} (Note that specimens characterised as ‘non-\textit{P. falciparum}’ are not sufficient). If analytical sensitivity is not detected in all relevant species of \textit{Plasmodium} species, then this limitation of the IVD should be clearly reported as a warning to the user in the instructions for use.</td>
<td>CLSI EP17-A2 (4)  Class II Special Controls Guidance document, FDA (7)  WHO Prequalification – Diagnostic Assessment (6)  Malaria Rapid Diagnostic Test Performance (8)  ELISA SOPs (9)</td>
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<td><strong>1.6.2 Validation of assay cut-off</strong></td>
<td>Malaria RDTs are generally qualitative and do not use a numerical value of assay cut-off. Nevertheless, the way in which the IVD was designed to differentiate positive specimens from negative specimens shall be demonstrated.</td>
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### 1.6.3 Measuring range

The potential for a prozone/high-dose hook effect shall be determined using several *Plasmodium*-positive specimens, for each claimed antigen, tested in several replicates at two different concentrations (diluted by at least a factor of 10).

**Notes on testing requirements**

1. Specimens shall be chosen that have a high antigen concentration, as estimated using microscopy or polymerase chain reaction (PCR).

### 1.7 Analytical specificity

#### 1.7.1 Potentially interfering substances

The potential for false results (false negatives and false positives) arising from interference from, at least, the substances/conditions listed below shall be determined (see Comment 1).

- Minimum of 100 specimens
- Each substance/condition represented by at least 3-5 specimens from different individuals.

Testing shall be undertaken in both *Plasmodium*-negative and -positive specimens unspiked or spiked with each potentially interfering substance at physiologically relevant dosages.

**Notes on testing requirements**

1. The risk assessment conducted for an IVD should identify substances where the potential for interference can reasonably be expected for the analyte being detected (e.g. PfHRP2, pLDH, etc).
2. Any observed interference shall be investigated and performance limitations of the IVD reported in the instructions for use. Results shall be reported with respect to each condition and not be reported as an aggregate of the total number of specimens tested in the study.

**Source documents**

European Commission (10)
CLSI EP07-A2 (11)
Class II Special Controls Guidance document, FDA (7)

#### 1.7.1.1 Endogenous

- Human antibodies to the expression system (for recombinants), e.g., Anti-*Escherichia coli* (anti-*E. coli* positive), Human anti-mouse antibody (HAMA)
- Recipients of multiple blood transfusions, pregnant (including multiparous) women.
- Elevated levels of haemoglobin, lipids, bilirubin and protein
- Elevated IgG and IgM
- Rheumatoid factor
- Other autoimmune conditions.
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| 1.7.1.2 Exogenous | • Relevant medicines, including: antiparasitic, antimalarial, antiretroviral and anti-tuberculosis medications  
• common over-the-counter anti-inflammatory medications (aspirin, paracetamol, ibuprofen)  
• ethanol, caffeine. | | |
### 1.7.2 Cross-reactivity

Determination of the potential for false results arising from cross-reactivity for a total of a minimum of 200 specimens, for at least 3-5 each of:

- viral infections, including: HIV, hepatitis B, C infection, acute hepatitis A infection, dengue, yellow fever virus post-immunization, measles, influenza A and B, tick borne encephalitis
- bacteria/parasites, including: Trypanosoma cruzi, Leishmania sp., Leptospira sp., Treponema pallidum, M. tuberculosis, Schistosoma sp., Toxoplasma gondii, Brucella sp.
- other unrelated conditions known to cause cross-reactivity.

1. The types of potential cross-reacting organisms tested for should be risk-based, taking into consideration the operational setting as well as the intended users.
2. Where either the scientific literature and/or risk analysis identifies the potential for false results in co-infected individuals (e.g. decreased sensitivity or specificity), further investigation shall be undertaken using *Plasmodium*-negative and -positive specimens.
3. Any observed interference shall be investigated and performance limitations of the IVD reported in the instructions for use.
4. Results shall be reported with respect to each condition and not be reported as an aggregate of the total number of specimens tested in the study.

### 1.8 Metrological traceability of calibrators and control material values

1.8.1 Metrological traceability of calibrators and control material values

The traceability of an external control to a validated reference material shall be demonstrated.

WHO encourages the use of external / quality control specimens which shall be traceable to a validated reference material and demonstrate whether a test result is valid. Where a malaria RDT uses a procedural control either in addition to, or instead of, an external control, the extent to which the presence or absence of this band corresponds to a valid test shall be demonstrated.

### 1.9 Stability

1.9.1 IVD stability

Replicate testing shall be undertaken using a panel consisting, for each claimed analyte, of at least:

- 1 analyte non-reactive specimen
- 2 low-reactivity specimens near assay cut-off
- 1 medium-reactivity specimen.

Where possible, specimens chosen for the testing panel shall include panel members that reflect the main specimen types intended for use with the IVD (e.g. capillary whole blood).

1. The testing panel shall include all claimed antigens (e.g. PfHRP2, pLDH, etc.) and, where ‘pan-specific’ detection is claimed, address stability in relevant *Plasmodium* species.
2. Testing shall include whole blood specimens in accordance with intended use (for example to verify proper flow, no background interference and account for other variables).
3. Lots shall comprise different batches of critical components.
4. Low-reactivity specimens shall be chosen that are

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ISO 23640:2011 (12)
CLSI EP25-A (13)
Technical Guidance Series for WHO Prequalification – Diagnostic Assessment (14)
ASTM D4169-14 (15)
1.9.2 Shelf life

- Real time studies using a minimum of 3 lots of final design product
- Transport stressed (simulated) before real time studies are undertaken
- IVD in final packaging also subjected to drop-shock testing.

- Sufficiently close to the assay cut-off as to allow changes in IVD sensitivity to be detected.

5. The numbers of invalid tests shall be reported.

6. Determination of shipping stability shall be performed using simulated extreme stress conditions, ensuring that application of those conditions is consistent and controlled.

7. Claims for stability shall be based on the second-last successful data point from the least stable lot, with, if lots are different, a statistical analysis showing that the bulk of lots will be expected to meet the claimed life. For example: for testing conducted at 3, 6, 9, 12 and 15 months, if stability was observed at 15 months, then the maximum stability claim is 12 months.

8. Accelerated studies do not replace the need for real time studies.

9. In-use stability of labile components shall be conducted using components in their final configuration.

1.9.3 In-use stability

- Minimum of 1 lot using panel(s) compiled as above
- Testing of all labile components (e.g. buffers vials, sealed cartridges, etc.; see Comment 9).

1.10 Flex studies

1.10.1 Flex studies

The influence of the following factors on expected results shall be considered:

- Temperature (see Comments 1 & 2)
- Reading time (i.e. the interval between when the first and last readings may be taken)
- Specimen and/or reagent volume
- Buffer pH
- Buffer concentration (to account for evaporation, whether in single- or multiple-use containers)
- Lighting and humidity.

1. Refer to WHO document PQDx_018 “Instructions for compilation of a product dossier” for other flex studies that may be relevant, taking into consideration the broad range of operational and environmental conditions consistent with intended use.

2. If use of an IVD relies on particular operational conditions (e.g. temperature), these shall be reported in the instructions for use.

3. The factors listed opposite should be investigated in ways that not only reflect but also exceed likely operating conditions in lower- and middle-income countries so that the limitations of the device to be understood. For example, in addition to investigating deviations of temperature within those claimed in the instructions for use (in the middle and at both lower and upper extremes of a claimed temperature range), temperature ranges should...
be investigated that exceed those of claimed operating conditions and which cause test failure (incorrect/invalid results).
### Part 2 Establishing clinical performance characteristics

<table>
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| **2.1 Diagnostic sensitivity and specificity** | Diagnostic sensitivity and specificity shall be determined principally in capillary whole blood. Testing should be conducted:  
• at different geographical and epidemiological settings representative of intended users (minimum of 2 regions)  
• by a variety of intended users (i.e. 9 - 12 users)  
• using more than 1 lot. | 1. Prequalified malaria RDTs will generally be used by trained lay providers and trained health care workers. For WHO prequalification purposes, these should also be considered as the intended user in addition to a laboratory professional.  
2. A separate, venous whole blood specimen shall be collected in parallel to establish the reference result. The testing algorithm used to determine the reference results should include PCR. Justification for the use of the testing algorithm shall be provided.  
3. Lots (design locked-down) shall comprise different batches of critical components.  
4. All discrepant results (between assay under evaluation and the reference results) shall be repeated on the same lot, and then on all available lots and the variability noted. Performance characteristics shall be reported using initial results only. The results of further testing of specimens with discrepant results shall be reported separately as additional information about IVD performance.  
5. All invalid results shall be recorded and evaluated in comparison to the reference result. Invalid results should be analyzed separately in the final performance calculations.  
6. Estimates of diagnostic/clinical sensitivity and specificity shall be reported with 95% confidence intervals.  
7. Where an IVD is intended to detect multiple analytes without differentiating which analyte is detected, specimens chosen for the testing panel shall comprise those that are reactive | European Parliament (19)  
WHO Technical Report Series (16)  
FDA (17) |
| **2.1.1 Diagnostic Sensitivity** | For IVDs intended for detection of *P. falciparum*:  
• at least 400 confirmed *P. falciparum*-positive specimens from a symptomatic population.  
For IVDs intended for detection of *P. vivax*:  
• at least 100 confirmed *P. vivax*-positive specimens.  
Where a claim is made for 'pan-specific' detection of Plasmodium species, performance characteristics shall be determined in each species for which specimens are available. At a minimum this shall include detection in specimens positive for *P. falciparum* and *P. vivax* (Note that specimens characterised as ‘non-*P. falciparum*’ are not sufficient). Where testing in these specimens has not been undertaken, this limitation of IVD performance should be reported to the user as a warning in the instructions for use. |
## Technical Specifications for WHO Prequalification of malaria RDTs

### 2.1 Testing requirements

#### 2.1.2 Diagnostic Specificity

<table>
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<th>Testing requirements</th>
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<tr>
<td>Testing of:</td>
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<td>• at least 1000 <em>Plasmodium</em> negative specimens from a symptomatic population.</td>
<td>only for each individual analyte (i.e. PfHRP2, pLDH, etc., as appropriate).</td>
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<td>8. Results shall be reported with respect to each study site and not be reported as an aggregate of the total number of specimens tested to establish these characteristics.</td>
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</tbody>
</table>

#### Notes on testing requirements

- Only for each individual analyte (i.e. PfHRP2, pLDH, etc., as appropriate).
- Results shall be reported with respect to each study site and not be reported as an aggregate of the total number of specimens tested to establish these characteristics.

### 2.2 Qualification of usability

#### 2.2.1 Label comprehension study

Questionnaire-based testing of subjects shall be undertaken to assess ability of intended users to correctly comprehend key messages from packaging and labelling:

- understanding key warnings, limitations and/or restrictions
- proper test procedure
- test result interpretation.

Questionnaire shall be administered to at least 10 intended users, in order to demonstrate comprehension of key messages in each population described in Comment 2.

#### 2.2.2 Results interpretation study

Subjects shall interpret the results of contrived IVDs (e.g. static/pre-made tests) to assess their ability to correctly interpret pre-determined test results. Contrived tests shall be made to demonstrate the following potential test results:

- non-reactive
- range of invalid results
- reactive
- weak reactive.

Testing subjects shall consist of at least 10 intended users from two geographically diverse populations to validate the effectiveness of the labeling and instructions for use.

#### Source documents

- USAID and WHO (18)
- European Parliament (19)
- IEC 62366-1:2015 (20)
- Backinger CL and Kingsley PA (21)
| Demonstrate correct interpretation of simulated test results. |   |   |
References


Technical Specifications for WHO Prequalification of malaria RDTs


List of related WHO Publications of related interest

WHO Prequalification Team - Diagnostic Assessment. Technical Guidance Series for WHO Prequalification – Diagnostic assessment (available online)

WHO Prequalification Team – Diagnostic Assessment. Instructions for Compilation of a Product Dossier. WHO document WHO/PQDx_18 (available online)
The Technical Specifications Series for submission to WHO Prequalification – Diagnostic Assessment set out appropriate performance evaluation criteria to meet prequalification requirements. Each Technical Specification provides information on the minimum performance requirements for WHO prequalification that should be met by a manufacturer to ensure that their in vitro diagnostic medical device is safe and performs optimally.

Further information on these and other WHO publications can be obtained from WHO Press, World Health Organization, 1211 Geneva 27, Switzerland

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