

# Quality Assurance of Malaria Rapid Diagnostic Tests

*Buying well and maintaining accuracy*

## Aim

This note has been developed to update personnel coordinating malaria diagnostics programmes based on current materials and WHO recommendations regarding the use of malaria rapid diagnostic tests (RDTs), and upcoming future developments. It contains information useful for guiding procurement decisions, and for developing funding proposals and implementation plans.

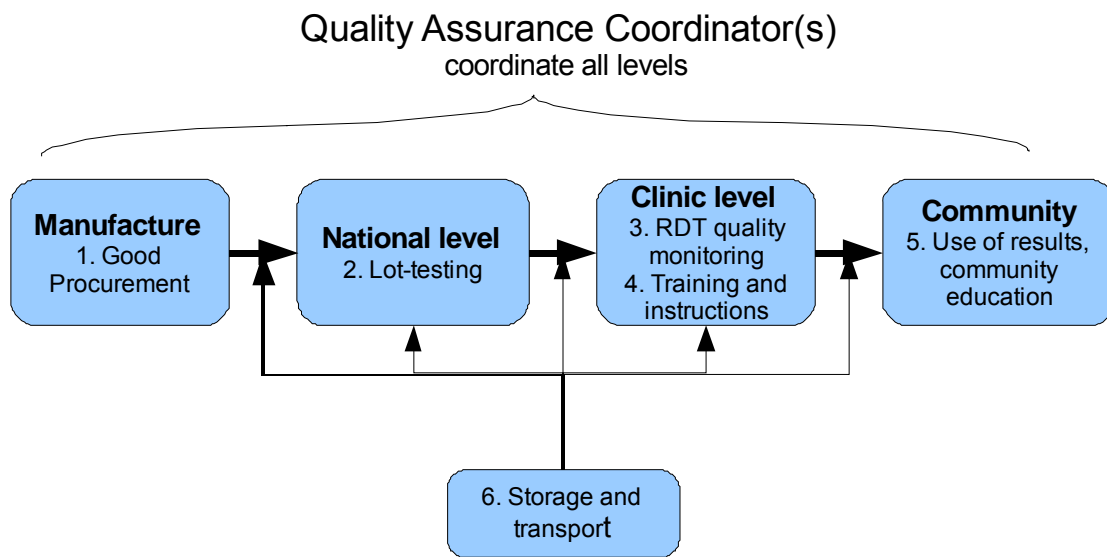
## Background

The introduction of malaria RDTs into control programmes is consistent with WHO recommendations that malaria case management be based on demonstration of parasites in most cases.<sup>1</sup> Malaria RDTs, when used well, can provide a rapid and reliable way to demonstrate the presence or absence of malaria parasites at all levels of the health service. However, evidence exists that current test accuracy in the field is variable, due to poor manufacture or exposure to high temperatures during transport and storage, and that negative results are frequently ignored by health care providers. To be effective, RDT introduction must be carefully planned, and the quality of testing ensured and demonstrated. Once this is achieved, RDT results can guide therapeutic decisions.

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<sup>1</sup> WHO (2006). The role of laboratory diagnosis to support malaria disease management: Focus on the use of rapid diagnostic tests in areas of high transmission. Geneva, World Health Organization.

## Current Recommendations



### 1. Planning for RDT introduction

This requires a strategic plan with clear timelines to ensure that the various components of the RDT programme are in place at the right time. A *Quality Assurance Coordinator(s)* should be designated to oversee the overall implementation plan and ensure that all agencies involved understand the process and their particular roles, and that none are neglected. The programme budget must include a significant component for planning, training, quality assurance and logistics, in addition to procurement. An example, covering the minimum requirements, is included in Annex I.

### 2. Procurement

It is recommended to procure from manufacturers with ISO 13485:2003 compliance<sup>2</sup>. The WebBuy procurement list for RDTs is available through the WHO procurement system and the wider list of products ([www.wpro.who.int/sites/rdt](http://www.wpro.who.int/sites/rdt)) is currently based on these criteria. ISO 13485:2003 certification should provide evidence of consistency and quality in manufacturing, but does not confirm good product performance.

An example procurement algorithm is shown in Annex II. The steps in the algorithm should be followed sequentially, using the malaria RDT product table available at [www.wpro.who.int/sites/rdt](http://www.wpro.who.int/sites/rdt). The algorithm will rapidly reduce the list to a short-list suitable for procurement purposes. Answers can then be approached to provide the documentation regarding the remaining specifications in Box 1.

<sup>2</sup> Compliance to USFDA 21 CFR part 820 is similar, but clear evidence of adherence may be hard to obtain.

**Box 1. Selection of RDTs from an ISO 13485:2003-based short-list should then be guided by the following factors:**

- Plasmodium species to be detected (*P. falciparum* only, pan-specific or other species-specific).
- Sensitivity and specificity
- Thermal (temperature) stability in intended conditions of storage and use
- Ease of use
- Requirement for post-treatment testing of patients
- Cost

**The manufacturer should provide:**

- Evidence of viability of manufacturer
- Product support
- Sample products ...test for ease of use, etc.
- Agreement for replacement of failed product
- Appropriate packaging
- A good blood-transfer device

*Sensitivity and specificity* are difficult to assess, as they are dependent on the parasite density and other characteristics of the population tested, on RDT preparation and interpretation, and on the quality of the reference standard. Data on test accuracy should be obtained from the manufacturer, but it should be interpreted with caution. In order to evaluate test sensitivity and specificity, lot-testing and field monitoring are essential.

*Thermal stability* data should be obtained from the manufacturer and compared with conditions of intended transport, storage and use. The parasite density (antigen concentration) of the standard used to assess stability should be noted, as a heat-damaged RDT may still detect samples with high parasite density.

Staggered delivery is good policy (splitting delivery from the manufacturer into 2 or 3 batches several months apart), as it reduces the burden on central storage facilities, and allows new products to be received nearer the expected time of use, shortening storage times and effectively lengthening the shelf-life of the overall procurement.

### 3. Lot testing: Pre- and post-purchase

It is recommended that all lots (batches) of RDTs be tested before deployment to the field. A 'lot' to be tested is normally defined as a production run using a particular batch of monoclonal antibodies and nitrocellulose. They are normally defined by number by the manufacturer, and usually consist of 40,000 to 80,000 tests. Lot-testing can be done:

- (1) before purchase, directly arranged with the manufacturer and a lot-testing centre  
(note: WHO WebBuy can not arrange this)
- (2) after purchase, before distribution to the field

### Why lot-test?

- To record lot-lot variation in most products
- To ensure no damage has occurred during transport to country
- To convince clinicians / users / regulatory authorities that tests are working

Currently, lot-testing is readily accessible. Lot-testing capacity has been developed through a joint programme of the WHO and FIND (Foundation for Innovative New Diagnostics), and can be facilitated by WHO. It is currently performed at two lot-testing centres in the Western Pacific Region which can perform tests for any programme globally, and capacity is currently being developed for lot-testing in Africa. The WHO will provide information on additional lot testing laboratories, with full contact details as soon as they become fully operational.

Requests for more information related to lot-testing should be made to WHO/WPRO at: [mal-rdt@wpro/who.int](mailto:mal-rdt@wpro/who.int) and [belld@wpro/who.int](mailto:belld@wpro/who.int)

Lot-testing is currently conducted through the WHO-FIND network at no charge; however, the sending institution must cover transport costs. At least 2 weeks prior notice should be given before shipping the RDT tests.

Testing is performed on a sample of about 125 *P. falciparum*-only RDTs or 175 combined *P. falciparum* and pan-specific RDTs for each production lot in the order. The lot-testing centres follow procedures developed by WHO for this purpose<sup>3</sup>, and usually return initial results within 5 working days. Retained RDTs are then monitored every 3 months at close to the manufacturer's recommended maximum storage temperature and the procuring agency is informed of results throughout the shelf-life. Further detail can be found at [www.wpro.who.int/sites/rdt](http://www.wpro.who.int/sites/rdt)

## 4. Monitoring performance in the field

Field monitoring is difficult, partly due to the inherent problems of accuracy of field microscopy, with which RDTs must be compared. At present, the following procedure is recommended:

- Compare RDT results with expert light microscopy. RDTs and blood films (BF) should be taken from the same patients in selected health facilities where RDTs have undergone typical storage and distribution.
  - e.g. Every month, 40 RDTs (20 positive and 20 negative) should be cross-checked against the corresponding 40 BF obtained from the same patients and examined by an expert microscopist. Where >10% discordant results occur, a more detailed field evaluation should be rapidly performed or the remaining RDTs should be returned for laboratory testing (see 'lot-testing' above).
- Expert microscopy may be available at the 'sentinel' sites used for monitoring therapeutic efficacy of antimalarial medicines, or at the central/regional reference

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<sup>3</sup> WHO (2006). The role of laboratory diagnosis to support malaria disease management: Focus on the use of rapid diagnostic tests in areas of high transmission. Geneva, World Health Organization.

laboratory. It is important that the microscopists selected for the evaluation of RDT performance have high competency.

In addition, it is important to supervise the health workers performing RDTs on a regular basis at least every 3 months in order to

- evaluate health worker capacity of interpreting a set of prepared RDTs
- assess health worker technique in RDT preparation
- review diagnosis and treatment records
- ensure good blood safety practices are maintained
- ensure sufficient supplies are in place for management of malarial and non-malarial fever

## 5. Training and instructions for users

Appropriate training of health workers is needed prior to introduction of RDTs, and instructions should be clear, in locally-appropriate language, and tested. WHO and partners have developed generic job-aids and a training manual for health workers, based on trials with several partners in Asia and Africa. These materials are available in English and French, and can be adapted to other languages. Examples can be down-loaded from [www.wpro.who.int/sites/rdt](http://www.wpro.who.int/sites/rdt)

## 6. Use of results and community education

There is extensive evidence that RDT (and microscopy) results are frequently ignored when treatment decisions are made. To address this problem, it is essential to:

- Ensure and demonstrate the accuracy of the RDTs (through the quality assurance processes described above)
- Provide management algorithms for appropriate management of parasite-negative cases (non-malarial febrile illness), and train health workers in their use
- Provide health workers with the means to manage parasite positive and negative cases appropriately
- Educate (sensitize) the community on the importance of parasite-based diagnosis.

Malaria diagnostic programmes therefore require an approach that addresses fever management, not just malaria management. To have a successful programme, it is vital to move beyond a narrow malaria-only approach.

## 7. Storage and transport

Standard supply management procedures should be applied to minimize storage times and exposure to extremes of temperature, similar to those for the handling of drugs. These include staggered delivery of large purchases, "First Expiry, First Out" stock management, controlled-temperature centralized storage, and minimizing storage in peripheral facilities with no temperature control. Direct sun exposure should be avoided and transport coordinated to minimize exposure to temperatures exceeding the manufacturer's recommended storage temperature.

## Future development

### Malaria RDT product testing

Product testing of malaria RDTs will be underway by mid-2008. Testing will occur against a panel of geographically-diverse parasite-positive blood, and a parasite-negative panel, and include a thermal-stability test<sup>4</sup>. The specimen bank on which testing will be based is currently under development at CDC in Atlanta, USA, and sample collection is underway at malaria endemic sites in Africa, Asia and the Americas. This is a joint project between WHO/TDR, WHO/WPRO and FIND. The testing and dissemination of results will be overseen by WHO and results of test performance will be published in a similar manner to those for HIV, Hepatitis B and C virus, and syphilis rapid testing programmes of WHO.

### Malaria RDT prequalification

A pre-qualification programme for malaria RDTs is under development by WHO/EHT, in collaboration with WHO/GMP, WHO/TDR and WHO/WPRO. This will involve the review of documentation submitted by manufacturers, inspection of production facilities and RDT product testing. It is expected to be in operation within the next 2 years.

### Positive Control Wells

The WHO is collaborating in the development of stable, well-calibrated positive control wells, containing recombinant antigens and designed to allow testing of malaria RDTs at clinic or village levels. These positive control wells will enable rapid direct evaluation of RDT performance in remote locations without the need for cross-checking against expert microscopy. In addition, a panel of wells of different antigens is also under development for standardized testing to be carried out at national level, which could have application for national regulatory testing and pre- or post-purchase lot-testing. Positive control wells are expected to be available within the next two years; until that time the following systems can be used to evaluate RDT performance:

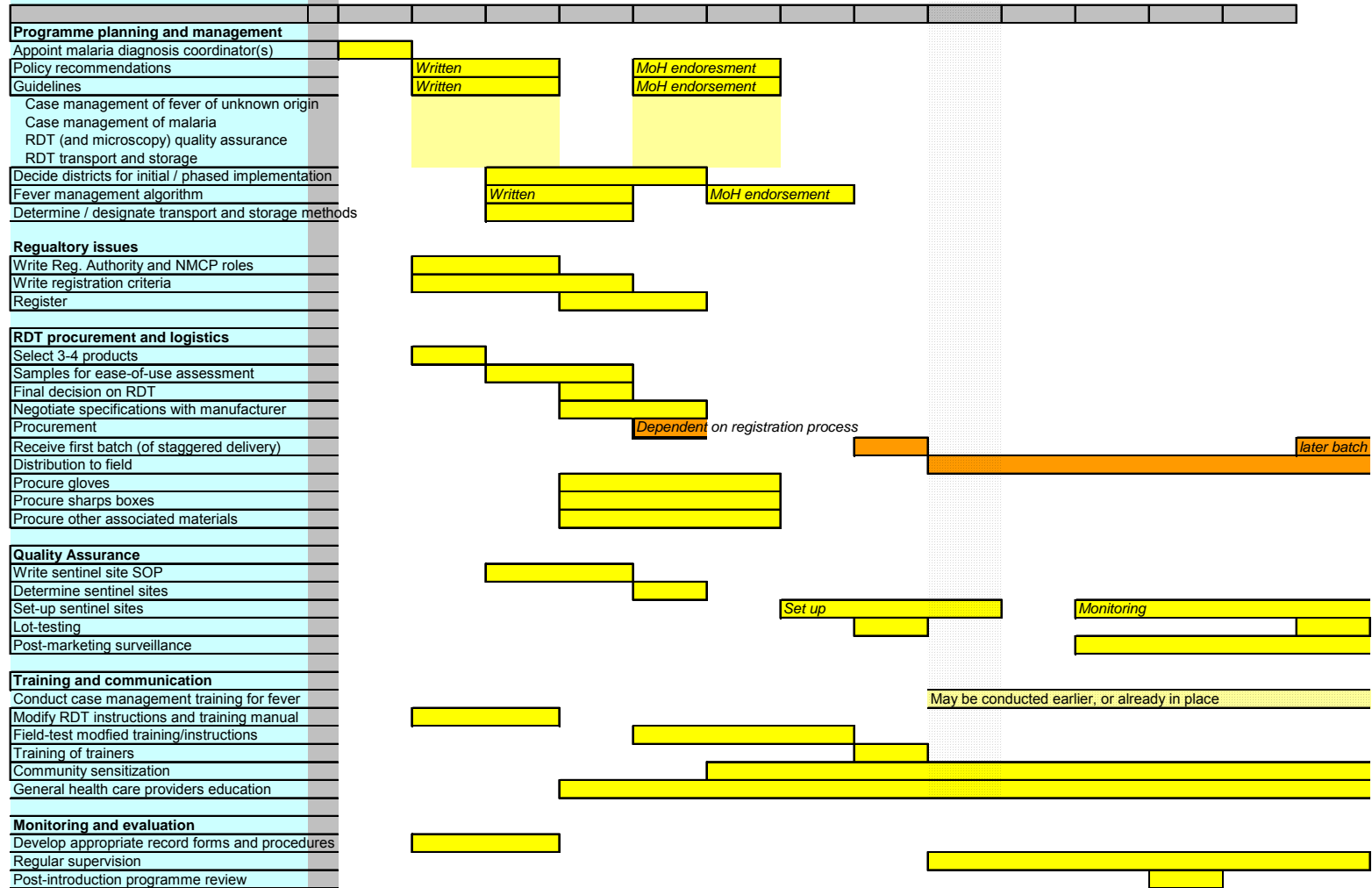
- 1) WHO-supported RDT pre- and post-purchase lot-testing in qualified centres, and
- 2) monitoring performance in remote areas requiring RDT comparison with microscopy.

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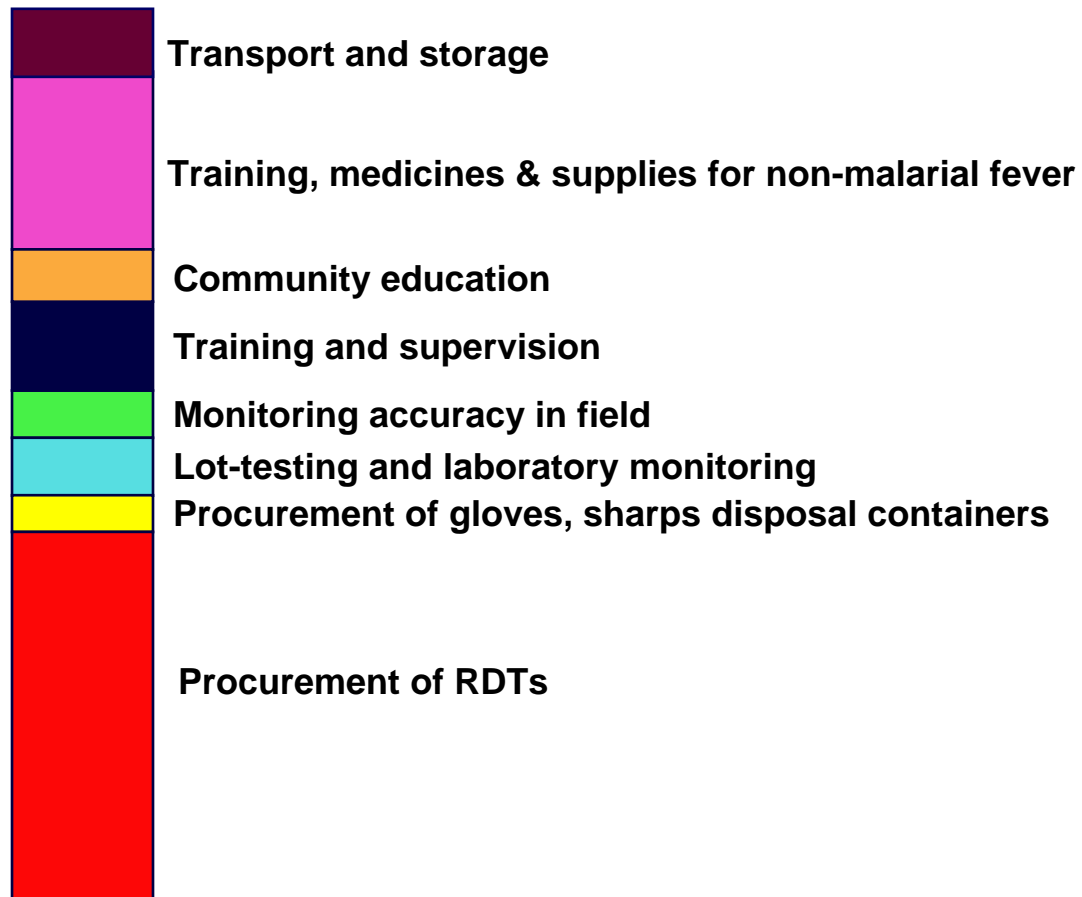
<sup>4</sup> WHO (2006b). Towards quality testing of malaria rapid diagnostic tests: Evidence and methods. Manila, World Health Organization.

# Annex I: RDT Implementation timelines and budgeting

**RDT IMPLEMENTATION TIMELINE** Example of necessary steps for implementation of Rapid Test (RDT)-based diagnosis in a national malaria programme.



## EXAMPLE OF BUDGETING DISTRIBUTION FOR A TYPICAL RDT-BASED DIAGNOSTIC PROGRAMME



Note: The distribution of funds will vary widely depending on the level of RDT use in the health system, and the logistical and support services already in place.

# Annex II: Short-listing RDTs for Procurement

(Commence with ISO 13485:2003-based product list: e.g. [www.wpro.who.int/sites/rdt](http://www.wpro.who.int/sites/rdt))

Parameter	Decision process	Decision
<p><b>1. Plasmodium species to be targeted</b></p>	<pre> graph TD     A[Distinguish non-Pf from Pf or mixed?] -- Yes --&gt; B[Combination test HRP2-pan pLDH HRP2-pan aldolase Pf pLDH-pan pLDH]     A -- No --&gt; C[Pf-only test HRP2 pLDH (may be combined with pan-specific pLDH)]             </pre>	<p>.....</p> <p>.....</p> <p>.....</p> <p>.....</p> <p>.....</p> <p>.....</p>
<p><b>2. Expected areas of use</b></p>	<pre> graph TD     A[Store and use in tropical/hit environment without temperature control] -- Yes --&gt; B[High-stability test Specified temperature e.g. &gt;=35°C]     A -- No --&gt; C[Storage temperature less critical Accept &lt;35°C specified storage]             </pre>	<p>.....</p> <p>.....</p> <p>.....</p> <p>.....</p> <p>.....</p> <p>.....</p>
<p><b>3. Likely clinical scenarios</b></p>	<pre> graph TD     A[Likely to use for re-testing soon after treatment / treatment-monitoring] -- Yes --&gt; B[Target non-persistent antigen pLDH-detecting for P. falciparum]     A -- No --&gt; C[Antigen persistence not critical HRP2 or pLDH for P. falciparum]             </pre>	<p>.....</p> <p>.....</p> <p>.....</p> <p>.....</p>
<p><b>4. End-user</b></p>	<pre> graph TD     A[For use by health workers outside medical laboratories] -- Yes --&gt; B[Simple format, all-inclusive Cassette design Lancet, swabs etc included in package]     A -- No --&gt; C[Design less critical Include dipsticks Test-only packaging]             </pre>	<p>.....</p> <p>.....</p> <p>.....</p>
<p><b>5. Other considerations:</b> Box size: How many fever cases expected in 3 months (if less than one box, request reduced box size)</p>		<p>.....</p> <p>.....</p> <p>.....</p>
<p><b>Next Step: Develop short-list of suitable RDTs</b> Highlight tests on WHO RDT Website list (ISO 13485-accredited manufacturers, or WebBuy list, if procuring within WHO system). Sometimes preferences will be incompatible, in which case, follow the general priorities of the numbered order above.</p>		

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## *Choosing specific products from the short-list*

If procuring through WebBuy, some of the above information will already be available

### **1. Contact Manufacturers**

Request:

1. Price (include delivery to country, and staggered delivery in 2-3 batches over 12 months)
2. Request heat stability data as evidence of manufacturer's stated storage temperature and shelf-life.
3. Request sample of product to assess format, ease of use, compatibility of other materials with health system requirements



### **2. Assess other experience**

If possible, obtain written assessments of field experience from other countries / programmes that have experience in using the product.



**Make preliminary procurement decision, then...**



### **3. Options to consider to improve implementation**

1. Negotiate replacement of product if fails lot-testing after delivery by method approved by manufacturer / WHO-coordinated laboratory.
2. Develop appropriately-formatted instructions in appropriate language consider inclusion in boxes at manufacturing site.
3. Negotiate delivery dates for staggered delivery to reduce in-country storage times.