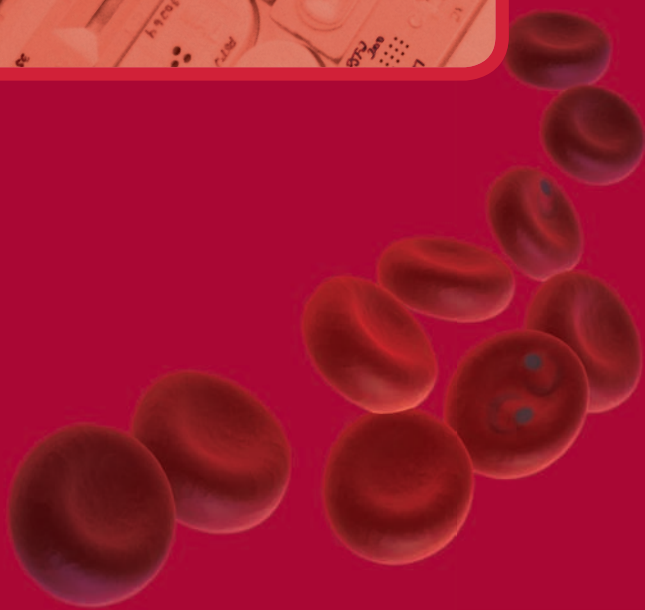




WHO Global Malaria Programme

Good practices for selecting and procuring rapid diagnostic tests for malaria



Good practices for selecting and procuring rapid diagnostic tests for malaria



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Please consult the WHO Global Malaria Programme web site for the most up-to-date version of all documents (www.who.int/malaria).

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User feedback is welcomed, and improvements will be considered. Feedback can be sent by e-mail to infofomp@who.int, indicating in the subject line: 'Comments on WHO good practices for selecting and procuring of RDTs'.

Abbreviations

FIND	Foundation for Innovative New Diagnostics
HRP2	histidine-rich protein 2
ISO	International Organization for Standardization
pan	all <i>Plasmodium</i> species
Pf	<i>Plasmodium falciparum</i>
pLDH	<i>Plasmodium</i> lactate dehydrogenase
Pv	<i>Plasmodium vivax</i>
Pvom	<i>Plasmodium vivax, ovale</i> and <i>malariae</i>
RDT	rapid diagnostic test
TDR	Special Programme for Research and Training in Tropical Diseases
WHO	World Health Organization

Glossary

Acceptance criteria: Measurable terms under which a test result will be considered acceptable; may be numerical limits, ranges or others (48).

Ancillary items: Items required to perform the RDT at point of use, such as the blood collection device (always in the box with the test kits), buffer and dropper (always in the box with the test kits), a sterile lancet (may be in the box) and an alcohol swab (may be in the box).

Antibody: Immunoglobulin with a particular amino acid sequence and tertiary structure that binds to a complementary structure on the antigen, called the epitope. The combining sites on the antibody and the antigen fit tightly together with a strong attractive force, because the matching areas on the surface of each molecule are relatively large.

Antigen: Substance that can elicit a specific immune response due to specific configurations (epitopes) on the surface of the high molecular mass molecules (e.g. proteins, polysaccharides and nucleic acids). The target antigens of malaria RDTs are proteins produced by malaria parasites. The RDTs on the market target aldolase, HRP2 and pLDH.

Authorization: See ‘Marketing authorization’.

Available shelf-life: The shelf-life available before expiry, expressed as the proportion of the stated shelf-life in days, weeks or months before expiry.

Batch: Defined quantity of product manufactured in a single process or series of processes and therefore expected to be homogeneous (49) (sometimes used interchangeably with ‘Lot’).

Batch number: Distinctive combination of numbers or letters, which uniquely identify a batch; for example, on labels, batch records and corresponding certificates of analysis (49).

Combination RDT: RDT with more than one test line, which detects *P. falciparum* and other malaria species (in different combinations).

Competent authority: Government agency with responsibility for standards of safety, quality and performance; instance of the wider definition of ‘any person or organization that has the legally delegated or invested authority, capacity, or power to perform a designated function’.

Container: Material used in packaging a product; includes primary, secondary and transport containers. Containers are referred to as ‘primary’ if they are intended to be in direct contact with the product and as ‘secondary’ if they are not intended to be in direct contact with the product (49).

Contract: Business agreement for the supply of goods or performance of work on the basis of mutually agreed terms and conditions (adapted from 49).

Control line: The line in the test window of a malaria RDT that becomes visible when the antibody bound to the control line binds to the dye-labelled capture antibody. Absence of the control indicates a problem with the test, and the result is invalid.

Detection rate: See ‘Panel detection score’.

Device master file: Detailed information on a product submitted to a regulatory authority, intended for incorporation into the application for marketing authorization (48 amended). See also ‘Product dossier’.

Expiry date: Date on a container (usually on the label) of a product up to and including which the product is expected to meet specifications, if stored correctly. The shelf-life as established by adequate stability studies is defined for each batch at the date of manufacture (49).

External quality assessment: A programme aimed at assessing the quality of the performance of laboratories or testing sites. It may include sending out proficiency panels and analysing the results, blinded rechecking of previous results, on-site visits to assess the laboratory’s operations, or a combination of the above (25).

False-positive rate: Percentage of all tests of a particular product that gave a positive result when it should not have, on the basis of the manufacturer’s recommended reading time (1).

Global Harmonization Task Force: A voluntary group of representatives from national medical device regulatory authorities and the regulated industry in Australia, Canada, Europe, Japan and the United States of America, who aim to harmonize basic regulatory practices to ensure the safety, effectiveness, performance and quality of medical devices (see <http://www.ghtf.org/>).

In vitro diagnostic device: A device, whether used alone or in combination, intended by the manufacturer for examination in vitro of specimens derived from the human body, solely or principally to provide information for diagnostic, monitoring or compatibility purposes. They include reagents, calibrators, control materials, specimen receptacles, software and related instruments or apparatus or other articles (50).

Incoterm: ‘International commerce terms’ are sales terms published by the International Chamber of Commerce and widely used in international commercial transactions; used to divide transaction costs and responsibilities between buyer and seller and reflect state-of-the-art transport practices (28). Incoterms 2010 applicable for all modes of transport include:

- EXW: ex works
- FCA: free carrier
- CPT: carriage paid to
- CIP: carriage and insurance paid to
- DAT: delivered at terminal
- DAP: delivered at place
- DDP: delivered duty paid

Incoterms 2010 applicable only for sea and inland waterway transport include:

- FAS: free alongside ship
- FOB: free on board
- CFR: cost and freight
- CIF: cost, insurance and freight

Invalid rate: Proportion of tests declared invalid.

Invalid test: Test in which the control line does not appear.

Labelling: Identification of a product, which should include at least the following information, as appropriate: name, target antigens, parasites detected, test format, batch number, expiry date, special storage conditions or handling precautions, directions for use, warnings and precautions, names and addresses of the manufacturer or supplier (49).

Lot testing: Quality control testing of a product lot (batch) after release from the manufacturing site.

Manufacture: All or any operations of purchase of materials and products, production, quality control, release of products and related controls (3, 49, 51). Some regulatory and other competent bodies might define ‘manufacture’ as a minimum set excluding some elements and combinations, such as purchase and repackaging.

Manufacturer: Any natural or legal person with responsibility for design or manufacture of a product with the intention of making the product available for use under his or her name, whether or not the product is designed or manufactured by that person him- or herself or on his or her behalf by another person (19). Company that produces, packages, repackages, labels or re-labels product (3).

Marketing authorization: Official document issued by the competent regulatory authority for the purpose of marketing or free distribution of a product after evaluation for safety, efficacy and quality. It must set out, inter alia, the name of the product, the intended functions and safe use, the shelf-life and storage conditions and packaging characteristics. It specifies the information on which authorization is based (e.g. “The product(s) must conform to all the details provided in your application and as modified in subsequent correspondence.”). It also contains the product information approved for health professionals and the public, the sales category, the name and address of the holder of the authorization and the period of validity of the authorization. Once a product has been given marketing authorization, it is included on a list of authorized products and is often said to be ‘registered’ or to ‘have registration’. Market authorization is occasionally referred to as a ‘license’ or ‘product license’ (3).

Notified body: A certification organization that the national (competent) authority of a Member State designates to carry out one or more of the conformity assessment procedures described in the annexes of the European Union Directives. The Medicines and Healthcare Products Regulatory Agency is the competent authority in the United Kingdom under the three medical device directives. A notified body must be qualified to perform all the functions set out in any annex for which it is designated. The designation may be restricted to specified types of devices or annexes.

Packaging: Any material, including printed material, used in the packaging of a medical device but excluding any outer packaging used for transport or shipment. Packaging materials are referred to as ‘primary’ or ‘secondary’ according to whether they are intended to be in direct contact with the product (52, 53).

Panel detection score: A score between 0 and 100, calculated as the proportion of times a malaria RDT gives a positive result on all tests from both lots tested against samples of parasite panels at a specific parasite density (i.e. four tests at 200 parasites per microlitre, two at 2000 parasite per microlitre). Invalid tests are excluded from the analysis (1, ANNEX 4).

Pan-species tests: RDTs which, by virtue of the antigens detected, cover all the known, common *Plasmodium* parasite species.

Parasitaemia: Presence of parasites in the blood. Malaria can be reported quantitatively as the number of asexual parasites per microlitre of blood or as the percentage of red blood cells infected with parasites.

Performance: Diagnostic performance, for the purpose of this manual, refers to laboratory-based evaluation to demonstrate consistent detection at low parasite densities (200 parasites per microlitre) of *P. falciparum*, *P. vivax* or both, with a low false-positive rate and a low invalid rate (1).

Point-of-care kit: RDT packaged with the ancillary items necessary for use at the point of care.

Prequalification: A process that includes assessment of product quality, service reliability and financial viability of suppliers. May include a series of processes to evaluate new suppliers, including product dossier review in relation to specifications, inspection of manufacturing facilities and other possible procedures, such as reference checks with past clients and international agencies,

test purchases in small quantities and other types of information gathering. The aim is to eliminate substandard suppliers from tendering, and, by limiting the tender to prequalified suppliers, prequalification expedites adjudication (adapted from 4).

Procurement process: The process of acquiring supplies from private or public suppliers or through purchases from manufacturers, distributors or agencies.

Procurement management unit: Team including the procurement executive, senior administrators, technologists, pharmacists and finance officers, who are responsible for the procurement process.

Product dossier: Detailed information on a product submitted to a regulatory authority, intended for incorporation into an application for marketing authorization (48). See also 'Device master file'.

Quality assurance: Wide-ranging concept covering all matters that individually or collectively influence the quality of a product; the totality of arrangements made to ensure that products are of the quality required for their intended use (3).

Quality monitoring: All activities undertaken to assure the quality of diagnostic products in the country of use, including receipt, storage, distribution, surveillance including lot testing, and reporting of deficient products. All activities to ensure that the products continue to conform with the manufacturer's established quality specifications during storage, distribution and use, including lot testing, reporting of deficient products and surveillance, as part of a quality assurance system (25).

Quantification: Estimating the quantities and frequencies necessary to fill the supply pipeline, avoiding stock-outs and unused or expired stocks, meeting the demands for RDTs in a specific region. Based on an understanding of the requirements for the region and consumption levels

Rapid diagnostic test (RDT): Qualitative or semi-quantitative in vitro medical device used singly or in small series, which involve non-automated procedures and are designed to give a fast result. For the purpose of this manual, RDTs are immunochromatographic lateral flow devices for the detection of malaria parasite antigens.

Reference standard: Any material intended for use in specified chemical and physical tests, in which its properties are compared with those of the product under examination and which is of certified characteristics adequate for its intended use.

Registration: Any statutory system of approval required at national level as a precondition for introducing a product onto the market (5).

Regulatory authority: National body that administers the full spectrum of regulatory activities for medical devices, including all the following functions, in conformity with national medical devices legislation:

- giving marketing authorization for new products and variations of existing products;
- laboratory testing for quality control,
- monitoring adverse reactions,
- providing device information and promoting rational device use,
- inspecting and licensing manufacturers, wholesalers and distribution channels to ensure required compliance with quality standards,
- enforcement operations, and
- monitoring device use (3).

Safety: A safe product is one that does not cause harm or injury, is associated with a low incidence of adverse reactions and significant side-effects when adequate instructions for use are followed and has little potential harm under conditions of widespread availability (5).

Sampling: Operation to obtain a representative portion of a product, on the basis of an appropriate statistical procedure, for a defined purpose, e.g. acceptance of consignments or batch release (49).

Sensitivity: Percent of patients with the infection who will have a positive result in the test under evaluation, determined from the result of the reference or 'gold standard' test (27).

Shelf-life: Period during which a product, if stored correctly, is expected to comply with the specifications determined in stability studies on a number of batches. Used to establish the expiry date of each batch (49 amended).

Specifications: List of tests, references to procedures and appropriate acceptance criteria (numerical limits, ranges or other) for the tests described; they establish criteria to which a product should conform in order to be considered acceptable for its intended use (49 amended).

Specificity: Percent of patients without the infection who will have a negative result in the test under evaluation, determined from the result of the reference or 'gold standard' test (27).

Stability: Ability of a product to retain its chemical, physical and use-related properties within specified limits throughout its shelf-life (49 amended).

Stability testing: Long-term accelerated (and intermediate) studies undertaken on batches according to a prescribed protocol to establish or confirm the re-test period (or shelf-life) of a product (49 amended).

Supplier: Person or company providing a product on request; includes authorized distributors and manufacturers and traders of prequalified products (49).

Test line: Line in the RDT test window displaying the results of the test for the presence of the target antigen(s).

Test window: Part of RDT where the test results are displayed as visible lines.

Total cost of acquisition: Aggregate amount of direct and indirect monetary costs of a diagnostic product related to its procurement, including the costs of reagents and other consumables, freight and shipping, customs clearance, insurance, in-country distribution and storage, quality assurance and quality control, training, validation of new diagnostic algorithms and installation, servicing, commissioning and maintenance of equipment, if applicable (25).

Validation: Proving and documenting that any process, procedure or method accurately and consistently leads to the expected results (48).

Introduction

Purpose of the manual and target audience

The aim of this manual is to provide guidance for the procurement of quality-assured malaria rapid diagnostic tests (RDTs) that reliably give accurate results. It is based on the results of WHO product testing of malaria RDTs (1) and on WHO-recommended criteria for procuring RDTs (2). The guidance provided is general and should be adapted to the local context.

The target audience for this manual includes procurement officers, malaria programme managers, health officers and supply chain managers responsible for selecting, procuring or assisting in the procurement of RDTs for malaria in the public and private sectors.

The manual summarizes information from publications on the quality of malaria RDTs that is readily accessible only by specialized procurement agencies. Its aim is to improve understanding of the following aspects of procurement:

- performance components and selection criteria,
- estimating quantity requirements and budgeting,
- defining technical specifications,
- managing tenders, adjudications and contracts,
- quality control through lot testing,
- supply management and product recalls, and
- monitoring supplier performance and managing product variations.

The manual does not cover the general aspects of procurement, which are dealt with extensively in other documents (3–5). Reference (3) is the guideline used by many funding agencies and United Nations agencies. This manual covers activities in the procurement cycle up to the receipt of goods at the port of entry. It does not cover in-country storage, transport or distribution, as these are covered in other manuals (6, 7). It describes good procurement practice in a non-prescriptive manner, providing checklists and covering technical issues.

Organization of the manual

- A list of **abbreviations** and a **glossary** of technical terms are included in the introductory part of the manual.
- A **procurement checklist** at the beginning of the manual lists 12 steps essential for the selection and procurement of quality malaria RDTs, indicating individuals or entities usually responsible for the corresponding step.
- **Steps 1–12** are discussed in detail in the main chapters of the manual, especially focusing on information on specific requirements for RDTs (**STEP 1**), technical specifications (**STEP 4**) and quality assurance and control (**STEPS 8 and 9**).

- The **text in bold italics with arrows** (➔) indicates practical tools or solutions to the main points/challenges described in the corresponding section.
- **Boxes** contain examples of topics in the text and other useful information.
- Recommendations for FURTHER READING and Internet sources are listed at the end of certain sections.
- **Suggested search terms** for the Internet are given where applicable; these can be used and entered in general search engines (e.g. Google TM), even if the site address has changed over time.
- **Cross-references** to specific sections of the manual are given in **BOLD CAPITALIZED FONT**.
- **References** to sources are given as numbers in brackets (x) throughout the manual and a table of references is provided before the Annex section. Where applicable, Internet addresses are listed for documents that are available online.
- **Annexes** expand on topics that may be of interest to certain readers, without interrupting the flow of the main document.
- The manual ends with an **Index**.

Malaria

Malaria is caused by a protozoan parasite of the genus *Plasmodium*, of which four species¹ cause disease in humans: *P. falciparum* (the most virulent), *P. vivax*, *P. malariae* and *P. ovale*. The infection is transmitted to humans through the bite of female anopheline mosquitoes. All malaria infections initially present as a febrile illness. Malaria is most prevalent in Africa and Asia, affecting approximately 225 million people and causing 781 000 deaths in 2009 (8).

In the second edition of the *Guidelines for the treatment of malaria* (9), WHO recommends prompt parasitological confirmation by microscopy or RDTs in all suspected cases of malaria, before treatment is started. Treatment solely on the basis of clinical suspicion should be considered only when a parasitological diagnosis is not accessible. Rapid, accurate diagnosis and appropriate treatment are crucial, as a delay of even a few hours in the management of malaria may have lethal consequences.

ROLE OF RAPID DIAGNOSTIC TESTS IN MALARIA DIAGNOSIS

Microscopy and RDTs are both adequate to diagnose malaria in febrile patients. Demonstration of the presence of malaria parasites is advised before treatment with antimalarial medicines, as diagnosis based solely on clinical symptoms is of poor accuracy and leads to overdiagnosis of malaria, waste of antimalarial medicines, an increased frequency of adverse side-effects and increased drug pressure on resistant parasites. Early exclusion of malaria can enhance early diagnosis and appropriate management of other, potentially severe causes of fever (2). Parasitological diagnosis improves malaria case detection and surveillance systems.

¹ Cases of human infection with *P. knowlesi*, a natural parasite of macaque monkeys, which is microscopically indistinct from *P. malariae*, have been documented in isolated forest areas of South-East Asia.

Rapid diagnostic tests for malaria

RDTs, sometimes called ‘rapid diagnostic devices’, facilitate the diagnosis of malaria by providing evidence of the presence of *Plasmodium*-specific proteins (antigens) in human blood. Although many products are available on the market, some can detect only one species (e.g. only *P. falciparum*), while others also detect further species of the parasite (i.e. *P. vivax*, *P. malariae* and *P. ovale*), in different combinations; nevertheless, the principles of these diagnostic tests are similar. Most RDTs detect malaria species-specific antigens² produced by parasites present in the blood of infected individuals; enough blood for the diagnostic test can usually be obtained from a finger-prick. As the RDTs detect an antigen of the parasite and not the antibodies due to the human immunological reaction, the result is not affected by impaired immunity (due to e.g. HIV infection or malnutrition).

The components of an RDT kit are described in **SECTION 4.3**. The parasite life cycle and production of malaria antigens detected by RDTs are described in **ANNEX 1**, and the mechanism by which RDTs act is summarized in **ANNEX 2**.

Determinants of test performance

The number of RDTs available on the market has grown rapidly since their introduction in the late 1990s. It is estimated that currently about 60 manufacturers worldwide produce over 200 different commercially available RDTs; an estimated 50–70 million tests were procured in 2008 and 90 million in 2009. As the quality of the products varies widely and regulatory control of diagnostic devices in malaria-endemic countries is often weak, procurement agencies face problems in selecting quality-assured RDTs with high diagnostic performance.

RDTs must reliably detect malaria parasites at the densities associated with the disease (see **SECTION 1.3.1**). The diagnostic performance of RDTs is influenced in particular by:

- the quality of the manufacturing process (see **TABLE 1**),
- the antigen threshold the RDT is designed to detect,
- the species of parasite,
- the density and strain of parasites present,
- the concentration of target antigen,
- the exposure of the test to extreme temperatures and relative humidity,
- the technique used in performing the test, and
- the correct interpretation of the results.

Several components of RDTs that are essential to good diagnostic performance are subject to vulnerability, which, depending on the situation, requires risk management. If, for instance, the RDT is vulnerable to high temperatures, it should be used only in areas with a temperate climate and be shipped under controlled temperature. Depending on the level of risk, systems such as product and lot testing, as discussed in this manual, can minimize the intrinsic vulnerability of the RDT and the risks related to procurement. **TABLES 1** and **2** summarize the potential risks, which, when associated with a specific selection and procurement scenario, can be related to actual risks.

² RDTs to detect antibodies that target malaria antigens, which are used to screen blood for evidence of recent infection, are not discussed here.

Table 1. Vulnerability of various components of rapid diagnostic tests for malaria

Component	Characteristics that can make a product vulnerable
Nitrocellulose membrane ^a	Variation in pore size (can affect flow of antibody–antigen complex and clearance of blood)
Signal antibody	Stability of conjugation to label (e.g. colloidal gold)
	Amount of antibody on strip (affects test line intensity)
	Purity
	Innate ability of selected antibody to bind specific target of interest and not others
	Antibody stability
	Consistency and variability in manufacture
Capture antibody	Ability to adhere to membrane
	Amount of antibody on strip (affects test line intensity)
	Purity
	Affinity of the selected antibody for the target antigen
	Specificity of the antibody for the target antigen
	Antibody stability
	Consistency and variability in manufacture
Buffer, lysing agent and additives	Composition (can affect the stability of antibodies, neutralize agents that cause false-positive reactions and control red cell lysis to release antigens)
	Viscosity (can affect assay reaction rate)
	Variation in composition can affect RDT performance (influence antigen–antibody binding) ^b
	Required volumes, packaging and unit dose of buffers can vary among RDTs
	The shelf life of the buffer may be different from that of the RDT
Cassette housing	Placing of sample well controls blood contact with the signal antibody and varies by device
	Compression of nitrocellulose membrane (can inhibit flow)
	Presence, absence and placement of evaporation holes (can affect flow and reduce late back flow) varies by device
Packaging	Packaging (must exclude humidity to avoid degradation of RDT)
Buffer volume	Number of drops of buffer solution (controls flow and sometimes lysis but does not control the speed of development of the results)
Blood volume	Amount of blood transferred to the RDT (can affect the availability of the target antigens if low volume, and can reduce the clearance of blood, reducing clarity of results, if excess volume)

^a The term ‘wick’ is used in relation to the nitrocellulose membrane, but this refers to the capillary action of an absorbent nitrocellulose pad.

^b Therefore, buffer solutions should not be changed for different lots.

Table 2. Vulnerability in procurement of rapid diagnostic tests for malaria

Step	Procurement vulnerability
Selecting an appropriate RDT	Selecting HPR2-detecting RDTs for areas of prevalent falciparum and non-falciparum malaria Selecting combination RDTs for areas with predominantly falciparum malaria
Quantification	Overestimating requirements Underestimating requirements
Budgeting	Underestimating costs of transport, storage and distribution Poor compliance with procedural requirements of funding agencies
Technical specifications	Lack of specifications on diagnostic performance requirements Missing information on RDT format Missing thermal stability requirements Missing requirements for completeness of kit
Procurement method	Open tender, leading to multiple offers not relevant to conditions of use and extended bid evaluation timelines Direct procurement from limited suppliers, leading to limited choices and risks for high prices and delays
Inviting tenders	Limited use of the assessment made by the WHO product testing programme
Contracts	Missing specifications on manufacturer's liability for replacement of delivery of defective products No reference to lot testing and its performance requirements No specification of temperature requirements for transport and storage No staggering of deliveries Wrong timing of deliveries in relation to malaria transmission season or training of health workers
Evaluating bid response	Assessment of diagnostic performance based on insufficient documentation submitted by the manufacturer No involvement of malaria RDT experts in assessing compliance of the product to technical specifications set in the tender No submission or evaluation of RDT samples submitted by manufacturers Poor evaluation of production capacity and financial viability of the supplier
Lot testing	Post-shipment lot testing performed after arrival in the country of use without specification of liability for replacement in contractual agreements with manufacturer
Transport and port clearance	No specifications to forwarding agent for temperature requirements during transport by air or sea (e.g. in refrigerated containers) No specifications to clearing agent for temperature requirements during port clearance and customs procedures Delays and demurrage costs due to insufficient preparation of port clearance procedures

Procurement checklist

The checklist below summarizes the sequence of steps in procuring quality-assured RDTs. Detailed information on each step is given in the subsequent sections of this manual. While the steps are shown sequentially, they do not necessarily occur one after the other (some may be concurrent), and not all the steps have to be repeated for each tender. It is most important that all the responsible bodies are well coordinated and that there is prompt, transparent information flow so that all the steps are executed in harmony. An example of minimum timelines required for the RDT procurement process is provided in **ANNEX 3**.

STEP 1	
Requirements for selecting rapid diagnostic tests	<i>Responsible entity</i>
Select an RDT appropriate to the parasite species prevalent in the areas of use. The selection should be based on WHO and national guidelines on required performance and test characteristics for different levels of use and the results of the WHO product testing for the specific RDT.	National malaria control programme
STEP 2	
Estimating needs	<i>Responsible entity</i>
Estimate the number of malaria cases and RDT requirements for back-up stocks at different levels of the supply chain. Estimate the order size and frequency of deliveries to maintain adequate stocks to meet requirements, avoiding stock-outs and over-stocking (with risk of unused, expired RDTs).	National malaria control programme, quantification and forecasting team, laboratory department, procurement department
STEP 3	
Budgeting and budget components	<i>Responsible entity</i>
Consider all budget requirements to obtain quality-assured RDTs, including operating expenses (distribution, supply management, information and communication, training, supervision, quality assurance, quality control, monitoring and reporting) and not merely the cost of procuring the RDTs.	National malaria control programme
STEP 4	
Defining technical specifications	<i>Responsible entity</i>
Provide comprehensive, detailed specifications for the selected product, so that the manufacturer receives a clear indication of all RDT requirements for the clinical user. Use all available supports, such as the Foundation for Innovative New Diagnostics (FIND) interactive guide (10), to ensure a detailed presentation of criteria that will enable selection of an RDT with appropriate diagnostic performance.	National malaria control programme
STEP 5	
Procurement method and tender documents	<i>Responsible entity</i>
Assemble your requirements and technical, commercial and quality evaluation tender criteria documentation from the preceding steps, conforming with the administrative and financial requirements of the agency funding the procurement of RDTs (as appropriate), and publish the tender according to the procurement method selected.	Procurement unit team members, with input on technical and quality aspects from national malaria control programme

STEP 6	
Inviting tenders	<i>Responsible entity</i>
Invite requests for proposals from manufacturers that have been independently assessed as having the competence and the capacity to meet the procurement requirements. The independent assessment should include the diagnostic performance of the product (preferably by WHO product testing). Determine whether product registration or authorization ^a is required in the country of receipt. ^a	Procurement management unit in consultation with regulatory authority
STEP 7	
Evaluating bids and awarding contracts	<i>Responsible entity</i>
Thoroughly check the specifications of the product offered against the requirements submitted in the tender documents. Then, check the supplier criteria (competence and capacity) with certification to ISO 13485:2003 (11) and documentation in the product dossier. Contracts may be awarded to suppliers that meet the criteria, with clear indications of terms and conditions for deliveries and liability.	Procurement management unit and national malaria control programme
STEP 8	
Quality assurance in procurement and use	<i>Responsible entity</i>
Ensure the quality of the procurement programme, including appropriate quality control, such as lot testing, through accredited laboratories.	Procurement management unit
STEP 9	
Quality control by lot testing^c	<i>Responsible entity</i>
Lot testing is the most important aspect of quality control to ensure that the lots of RDTs delivered fully meet the agreed requirements.	Procurement management unit, quality assurance officer
STEP 10	
Transport, port clearance and receipt	<i>Responsible entity</i>
Air or sea port clearance has many potential pitfalls and possible delays; careful planning is needed to avoid exposure of RDTs to high temperatures, with concerted preparation for handling at receipt, storage and distribution. Verification of the delivered product at receipt is recommended.	Procurement management unit, supply chain manager
STEP 11	
Monitoring	<i>Responsible entity</i>
Supplier performance should be assessed in relation to the responsibilities in supply, which should be described in detail in the tender documents and contracts so that the relationship between the supplier and the manufacturer and liabilities are clear. Regular system audits and open communication channels are particularly important in this respect.	Procurement management unit and national malaria control programme
STEP 12	
Continuous improvement	<i>Responsible entity</i>
Effective use of a comprehensive quality management system for information on deficiencies of any kind can result in steady, continuous improvement.	Procurement management unit and national malaria control programme

^a This might apply only in countries where there is formal registration of diagnostic products.

^b Registration of the product in the country can expedite later steps; this should be established at the same time as the manufacturer's competence and capability are assessed.

^c The contract with an inspecting agency is separate from that for procurement of RDTs, and the selection and contract award to the laboratory must be organized beforehand.

STEP 1

Requirements for selecting rapid diagnostic tests

To select an appropriate RDT for the area of intended use, the diagnostic needs of the health providers and the performance requirements of the RDT in the field should be defined. This step precedes quantification and provides the essential information for elaboration of the full specifications of the RDT to be procured (**STEP 4**).

Step 1 covers the main RDT selection criteria:

- target parasite species and antigens (**SECTION 1.1**),
 - performance of RDTs (**SECTION 1.2**),
 - WHO recommendations and national treatment guidelines (**SECTION 1.3**),
 - experience in use of RDTs and availability (**SECTION 1.4**), and
 - additional considerations (**SECTION 1.5**).
- ➔ **SECTION 1.6 summarizes the above requirements in a single flow chart.**

1.1 Target parasite species and antigens

The four human malaria parasites, *P. falciparum*, *P. vivax*, *P. malariae* and *P. ovale*, are distributed differently throughout the world, and certain antigens expressed by these parasites also vary from region to region. To select an appropriate RDT, it is therefore necessary to know the species of parasite present in the region of intended use, in order to determine the appropriate antigen(s) that the test should be able to detect. Malaria RDTs currently on the market detect the following parasite antigens in various combinations:

- histidine-rich protein 2 (HRP2),
- various subtypes of *Plasmodium* lactate dehydrogenase (pLDH), and
- aldolase.

Other target antigens might have to be considered in the next few years. The production of antigens by malaria parasites at various stages of the parasite's life cycle is described in **ANNEX 1**.

HRP2 is produced only by *P. falciparum*, while aldolase is produced by all four species and can therefore be used to identify all human malaria parasites. pLDH is also common to all four species and can be detected by antibody-binding antigen epitopes that are common to all species (pLDH-pan) or specific to the pLDH of a particular species (i.e. pLDH-Pf, specific to *P. falciparum*; pLDH-Pv specific to *P. vivax*; and pLDH-Pvom, specific to non-falciparum malaria species, i.e. *P. vivax*, *P. ovale* and *P. malariae*) (**TABLE 3**). While pLDH with sequences specific to *P. malariae* and *P. ovale* exist, commercial products that target these antigens are not yet available. RDTs specific for pLDH-Pvom have begun to appear commercially.

Table 3. Antigen targets of rapid diagnostic tests for malaria

Plasmodium species	HRP2	pLDH				Aldolase
		pLDH-Pf	pLDH-pan	pLDH-Pvom	pLDH-Pv	
<i>P. falciparum</i>	X	X	X			X
<i>P. vivax</i>			X	X	X	X
<i>P. malariae</i>			X	X		X
<i>P. ovale</i>			X	X		X

HRP2 – histidine-rich protein 2
 pLDH – *Plasmodium* lactate dehydrogenase
 Pf – *P. falciparum*
 pan – all *Plasmodium* species
 Pvom – *P. vivax*, *ovale* and *malariae*
 Pv – *P. vivax*

RDTs for malaria respond to testing needs at different levels of the health care system. They can be used to confirm a diagnosis of malaria at a peripheral health facility where microscopy is not available, or in facilities with laboratory services, to reduce the workload of malaria microscopy or to confirm a diagnosis at times when microscopy services are not available.

TABLE 4 shows the recommended choice of RDT in relation to the prevalence of malaria species in different parts of the world.

Table 4. Choice of rapid diagnostic test according to prevalence of malaria species

Zone	Recommended RDT	Rationale
ZONE 1		
Most areas of sub-Saharan Africa and lowland Papua New Guinea <i>Prevalent parasites:</i> predominantly <i>P. falciparum</i> , with rare non-falciparum <i>Malaria infections:</i> Majority of non-falciparum infections occur as mixed <i>P. falciparum</i> infections, rarely as single-species infections	RDTs that detect only <i>P. falciparum</i> are generally preferable. <i>RDT target antigens:</i> • HRP2 • pLDH-Pf	Generally better thermal stability HRP2-detecting RDTs in general are likely to be more sensitive than pLDH- and aldolase-detecting RDTs for <i>P. falciparum</i> infections in most environments. ^a
ZONE 2		
Most endemic areas of Asia and the Americas and isolated areas in the Horn of Africa <i>Prevalent parasites:</i> <i>P. falciparum</i> and non-falciparum <i>Malaria infections:</i> <i>P. falciparum</i> and non-falciparum infections, commonly occurring as single-species infections	Combination RDTs that detect all species and distinguish <i>P. falciparum</i> from non-falciparum infections (Inappropriate to use RDTs that detect only <i>P. falciparum</i> , as this would require that RDT negative patients are treated with chloroquine for possible <i>P. vivax</i> infection, instead of being recognized as non-malaria cases) <i>RDT target antigens:</i> • HRP2, aldolase • HRP2, pLDH-pan • HRP2, pLDH-Pv • HRP2, pLDH-Pvom • HRP2, pLDH-pan, pLDH-Pv • pLDH-Pf, pLDH-pan • pLDH-Pf, pLDH-Pv • pLDH-Pf, pLDH-Pvom	HRP2-detecting tests in general are more sensitive than pLDH- and aldolase-detecting tests for <i>P. falciparum</i> infection in most areas. Some RDTs are highly sensitive for detecting both <i>P. falciparum</i> and <i>P. vivax</i> . Sensitivity for the detection of <i>P. ovale</i> and <i>P. malariae</i> is generally lower. First-line treatment for <i>P. falciparum</i> and for non-falciparum is different; therefore it is important to choose a test that distinguishes them. Low-density non-falciparum infections may be missed.

Table 4. Continued

Zone	Recommended RDT	Rationale
ZONE 3 ^b		
Mainly <i>vivax</i> -only areas of East Asia, central Asia and South America, and some highland areas elsewhere <i>Prevalent parasites:</i> non-falciparum malaria only <i>Malaria infections:</i> generally <i>P. vivax</i> malaria only	RDTs that detect non-falciparum species alone are appropriate (pan-specific, or <i>P. vivax</i> -specific if only species). <i>RDT target antigens:</i> • aldolase • pLDH-pan • pLDH-Pv • pLDH-Pvom	In several countries, falciparum malaria is not present, and treatment of all non-falciparum malaria infections is similar. In these areas, use of pan-specific RDTs is appropriate.

^a Most commercial RDTs (frequently pLDH-pan or aldolase) do not distinguish mixed infections from falciparum-only infections; therefore, the only advantage of using a combined RDT is to detect rare infections with non-falciparum parasites. As HRP2 tests are usually more sensitive for Pf, these are usually chosen.

^b If zones 2 and 3 co-exist in any part of the same country, combination RDTs that distinguish *P. falciparum* from non-falciparum infections are preferable for the whole country, in view of population movement.

1.2 Performance of rapid diagnostic tests

1.2.1 WHO RDT product testing

In view of the inherent variation in the results of field studies in different settings and the difficulty of assessing large numbers of RDTs in field trials, WHO, in collaboration with the Special Programme for Research and Training in Tropical Diseases (TDR), FIND and the Centers for Disease Control and Prevention, Atlanta, Georgia, USA, established in 2006 a programme for testing malaria RDT products. A standardized laboratory-based evaluation is made of the diagnostic performance of the tests, and the performance results obtained can be used to guide procurement decisions by governments and international agencies and to encourage improvements in the quality of RDTs. The programme is based on a network of laboratories that contribute parasite specimens to a global malaria specimen bank at the Centers for Disease Control and Prevention, which are used to assess malaria RDT performance. Some of the centres also serve as quality control centres for the WHO lot-testing programme (see **STEP 9**), and most also conduct national quality control of RDTs.

The parameters assessed in performance testing are:

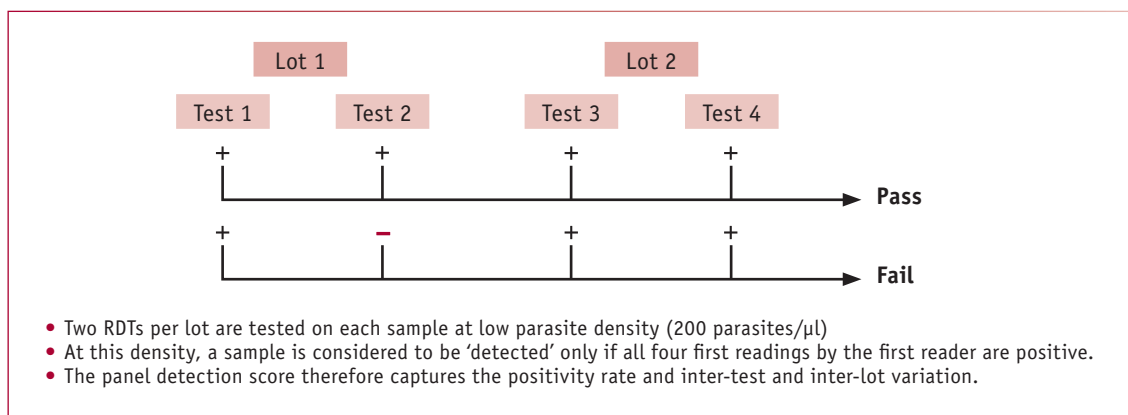
- the panel detection score (which should be 200 parasites per microlitre),
- the false-positive rate, and
- the invalid rate.

In addition, the programme provides comparative data on:

- ease of use (including completeness of the kits), and
- heat stability after 2 months at 35 °C and 45 °C at 75% humidity.

The ‘panel detection score’ (called the ‘detection rate’ in the first round of testing (12, 13) is a composite index of test positivity and inter-test and inter-lot consistency in performance. The score is not equivalent to sensitivity (1). As shown in **FIGURE 1**, the panel detection score is a number between 0 and 100, calculated as the proportion of times a malaria RDT gives a ‘pass’ result in all tests on both lots tested in multiple samples of parasite panels at a specific parasite density, i.e. four tests at 200 parasites per microlitre and two at 2000 parasites per microlitre. In round 2, the panel detection score at low parasite densities was calculated against panels derived from 100 samples of *P. falciparum* and 40 samples of *P. vivax*. Invalid tests are excluded from the analysis. In the calculation of the score for low parasite densities, all four tests (two each from two

FIGURE 1

**Determination of panel detection score at low parasite density
(200 parasites per microlitre)**

different production lots) should be positive in order for the test to 'pass'. In the example shown in the figure, the test 'fails' to detect parasite in a given sample if three of four tests are positive.

The panel detection score is different from the sensitivity or positivity rate, as it includes a measurement of intra-lot consistency and inter-lot variation. Thus, a score of 80% at a parasite density of 200 per microlitre is a good result and does not correspond to a sensitivity of 80% observed in the field. The largest difference in test performance that allows differentiation of RDTs that perform well and those that perform poorly is reflected in the panel detection score at the lower parasite density (200 parasites per microlitre).

The 'false-positive rate' is reported against a panel of clean-negative samples. The 'invalid rate' is the proportion of tests declared invalid, i.e. absence of the control line.

Rounds 1 and 2 of WHO RDT product testing provided performance results for 68 malaria RDTs available on the market (1). Tests with high panel detection scores for both *P. falciparum* and *P. vivax* were identified in both rounds. In addition, a series of tests showed good correlation among all the parameters: high panel detection score at 200 parasites per microlitre; low false-positive rate; low invalid rate; high level of ease of use; and high thermal stability. A high panel detection score was not correlated with a high false-positive rate. Round 3 will involve evaluation of 50 products.

Any evaluation is a 'snapshot' in time and may not represent the characteristics of future lots of the same product, especially in the context of manufacturing scale-up. This underscores the importance of lot testing (STEP 9).

1.2.2 Sensitivity and specificity

The performance of malaria RDTs can be assessed from their diagnostic sensitivity and specificity, as reported in the scientific literature (see SECTION 1.2.1), but the quality of studies is variable, and the results likely to be specific to the study population.

The published results of RDT field trials vary in sensitivity and specificity, because of:

- the parasite density in the study population (RDT sensitivity depends on the antigen concentration and decreases at low parasitaemia levels),
- heterogeneous diagnostic performance of the comparison method (usually microscopy),
- inconsistent manufacturing standards for the RDT used in the study,

- exposure of the test to high temperatures during distribution and storage before the study, and
- problems with test preparation or interpretation of results.

Use of values for sensitivity and specificity from comparative studies is problematic and in general does not result in the selection of products with high diagnostic performance. The methodological problems may be even more severe in unpublished reports submitted by manufacturers as proof of good diagnostic performance.

➔ ***It is preferable to base the choice on the results of the most recent round of WHO product testing of malaria RDTs (SECTION 1.2.1) and to use the results of field studies as a complementary source of information.***

PANEL DETECTION SCORE IN RELATION TO SENSITIVITY

The *panel detection score* is a standardized measure of RDT performance, which is centrally and impartially administered and which meets the strictest standards of laboratory testing, whereas *sensitivity* and *specificity* are not standardized and their values depend closely on samples selected for the study, RDT quality and storage conditions, and the user's skill in preparing and interpreting test results.

More information on the relations between specificity and sensitivity and the panel detection score is given in **ANNEX 4**.

1.3 WHO recommendations and national treatment guidelines

The procurement department should liaise with the national malaria control programme to obtain clear criteria for selecting an appropriate RDT, taking into consideration WHO recommendations on diagnostic performance of tests (**SECTION 1.3.1**)¹. WHO recommendations should be translated into national treatment guidelines, and the procured RDT should meet the requirements of the national guidelines (**SECTION 1.3.2**).

1.3.1 WHO recommended selection criteria for procurement of RDTs¹

It is the responsibility of each national malaria control programme to select RDTs that perform well for the setting of intended use. Experts convened at the Inaugural Meeting of the Malaria Policy Advisory Committee (MPAC), held in Geneva in early 2012, updated the WHO recommendations for the procurement of RDTs. Products should be selected in line with the following set of criteria, based on the results of the assessment of the WHO Malaria RDT Product Testing Programme:

¹ The text of chapter 1.3 in this reprinted version differs from the text of the original version, since the WHO Information note on recommended selection criteria for procurement of malaria rapid diagnostic tests (RDTs) has been updated following the expert recommendations as agreed at the Inaugural Meeting of the Malaria Policy Advisory Committee (MPAC) held in Geneva in early 2012. The full WHO information note is available at the internet via the following link:

http://www.who.int/entity/malaria/diagnosis_treatment/diagnosis/RDT_selection_criteria.pdf

1. For the detection of *P. falciparum* (Pf) and / or for the detection of *P. vivax* (Pv):
In all transmission areas, the Panel Detection Score (PDS) against Pf and / or Pv samples should be at least 75% at 200 parasites/ μ L.
2. False positive rate less than 10%
3. Invalid rate less than 5%

When the above criteria are fulfilled, other considerations relevant for procuring malaria RDTs should be taken into account:

- *Stability requirements at temperatures of intended storage, transport and use:* RDTs submitted to WHO for malaria RDT product testing are evaluated for positivity against a single cultured *P. falciparum* isolate at 200 parasites/ μ L at baseline and after 60 days of incubation at 35°C and 45°C. In this regard, it is recommended to select RDTs with high thermal stability for areas with very high temperatures.
- *Ease of use and training requirements for the health workers:* RDTs submitted to WHO for malaria RDT product testing are also evaluated for blood safety, instruction quality, number of steps, time to results, blood transfer device, format and kit completeness. Cassettes and cards are easier to use than dipsticks. For reasons of blood safety, kits that include lancets and alcohol swabs are preferred over kits which do not contain these items. Dipsticks are more suitable for settings with a laboratory facility.
- *Price:* After having considered all of the above factors, good procurement practice requires that the price be taken into account.

As the performance of individual products is likely to vary between lots over time, WHO recommends that all production lots be checked by *lot testing* as part of good procurement practice (see **STEP 9**).

1.3.2 National treatment guidelines

The WHO guidelines for the treatment of malaria (9) should be reflected in the national treatment guidelines, adapted to the situations and requirements of the country. The national guidelines should provide guidance on diagnosis and treatment of malaria and include recommendations on the use of RDTs based on malaria prevalence, parasite species, health infrastructure and personnel, available malaria diagnostics (microscopy and RDTs), their distribution in different geographical areas and their availability at different levels of the public and private health care systems (hospitals, health centres, field clinics) up to community level. Procurement of malaria RDTs should be in line with the recommendations given in the national guidelines and national procurement policy.

1.4 Experience in use of rapid diagnostic tests and availability

Experience obtained with RDTs under the conditions of intended use, including the results of feasibility studies in the country, should be carefully considered when selecting an appropriate RDT. If feasibility studies cannot be performed before procurement of RDTs, documentation on ease of use should be obtained from other countries with similar conditions of use. This experience is more helpful for judging ease of use than for evaluating the performance of the tests because of the intrinsic variability in field trials (SECTION 1.2). Procurement should be guided by the needs of the national malaria control programme, taking into account the availability of RDTs in the country, their level of deployment, ease of use, completeness of the kits and training requirements for health personnel if a new type of RDT is to be procured.

The diagnostic performance of RDTs in the field depends on all the parameters listed above, as well as on the effectiveness of training and supervision and the functioning of the supply management system. Particularly in programmes in which RDTs are already being used on a large scale, continued use of current tests may be appropriate until a decrease in malaria transmission triggers the need for RDTs with better performance in detecting low-level parasitaemia. Plans to replace RDTs should be developed carefully, taking into consideration the training and supervision requirements to support the introduction of new RDTs, as well as the production capacity and expected lead time for deliveries from the suppliers of the new RDTs.

➔ *Experience obtained with RDTs under the conditions of intended use, including the results of feasibility studies in the country, should be carefully considered when selecting an appropriate RDT.*

1.5 Additional considerations

Further considerations essential for selecting appropriate RDTs are given in other sections of the manual:

- supplier's production capacity and lead times (STEP 7),
- storage conditions, delivery schedules and shelf-life (STEP 10),
- registration requirements by the national regulatory authorities (STEP 6),
- overall budget requirements, including operational costs (STEP 3; 13) .

With regard to STEP 6, registration of diagnostic products by medical device control authorities is often lengthy and might delay shipment and receipt of goods. Risk mitigation could include early registration as soon as the RDT is selected or choosing an RDT that is already registered. As the performance of individual products is likely to vary between lots over time, WHO recommends that all production lots be tested as part of good procurement practice (STEP 9). The WHO/FIND malaria RDT evaluation programme provides lot testing free of charge through accredited laboratories. (Full information on WHO recommended procedures for RDT lot testing is given in reference 14.)

1.6 Summary

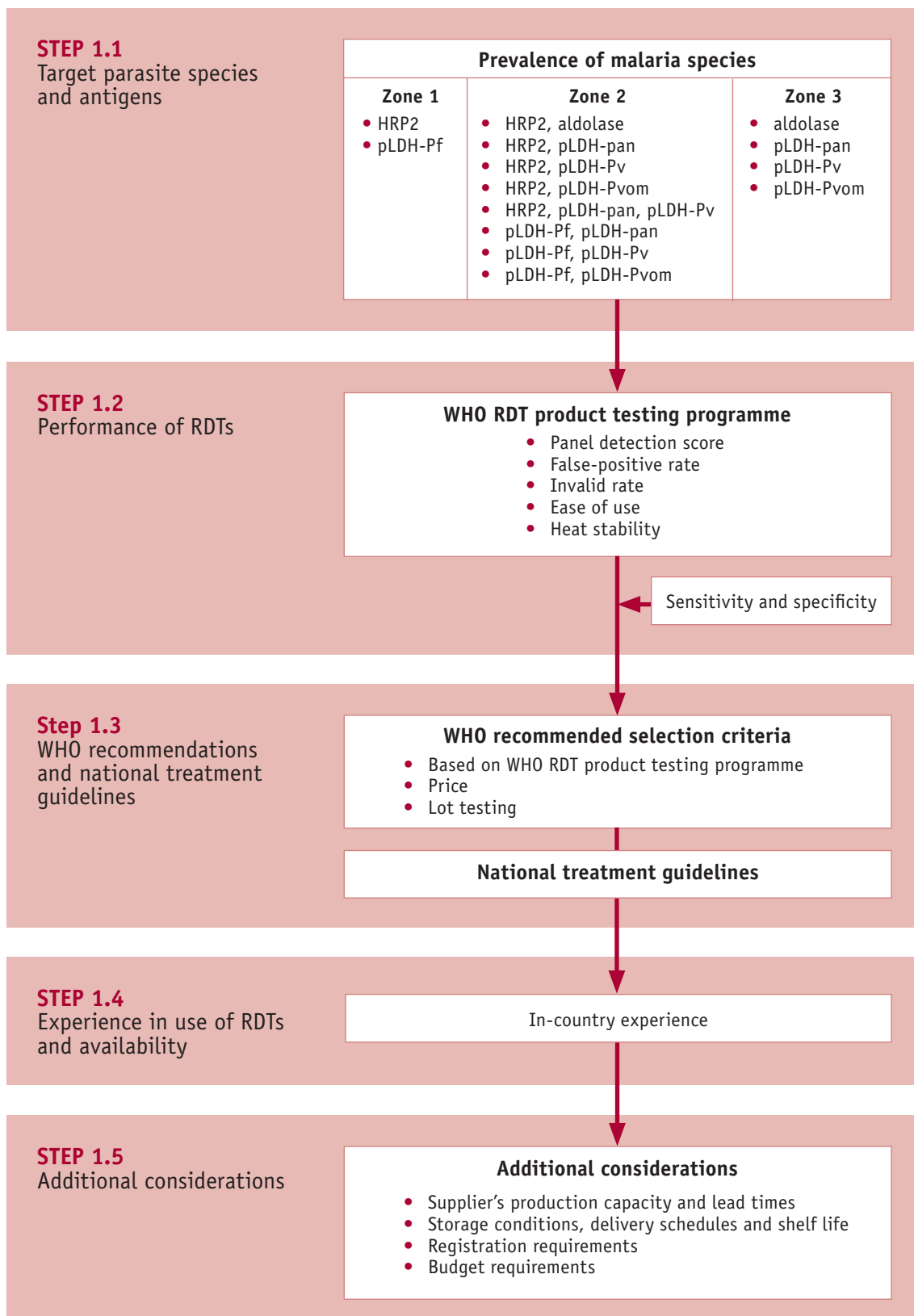
The flow chart in **FIGURE 2** summarizes the determinants described in **STEP 1** and the process for selecting an appropriate RDT for the intended area of use.

FURTHER READING

- *What is an RDT*. Manila, WHO Regional Office for the Western Pacific.
<http://www.wpro.who.int/sites/rdt/whatis/list.htm>
Search: “**what is an RDT**”
 - *RDT making it work*. Manila, WHO Regional Office for the Western Pacific, 2003.
http://www.searo.who.int/LinkFiles/Malaria_MalariaRDT.pdf
Search: “**RDT making it work**”
 - *Methods manual for product testing of malaria rapid diagnostic tests (2009)*. Foundation for Innovative New Diagnostics, Geneva.
http://www.finddiagnostics.org/export/sites/default/programs/malaria/docs/methods_manual_malaria_rdt_testing_version2a.pdf
Search: “**Methods manual for product testing of malaria RDTs 2009**”
-

FIGURE 2

Selection of an appropriate RDT for the intended area of use



STEP 2

Estimating needs

STEP 2

Estimating requirements is a critical step in procurement. The step comprises quantification and forecasting and should be guided by information from a logistics management and information system. This step may be challenging and requires collaboration within a multidisciplinary, multi-stakeholder team with a responsible person.

2.1 Quantification

The first action for the national malaria control programme is to allocate responsibility for quantification to a competent person or team with relevant experience, who will produce a plan based on needs (central or local, depending on the levels of use within the health care system). The team might include senior medical administrators, clinicians or technologists, managers of the health information system, pharmacists and a finance officer. External technical assistance can be brought in. Over time, large-scale deployment of RDTs will affect the consumption of artemisinin-based combination therapies; therefore, the membership of the teams involved in quantifying RDTs and antimalarial medicines should overlap significantly in competency and scope of work.

The second action is to define the target area in terms of requirements for and distribution of RDTs, including all storage and distribution points, and the health delivery services that will use them (e.g. hospitals, health centres, dispensaries, health units, health posts and community workers).

The approach used for quantification depends on whether the area has:

- no malaria surveillance data (e.g. emergency use or new community case management programmes; **SECTION 2.1.1**),
- unreliable malaria surveillance data (**SECTION 2.1.2**),
- reliable malaria surveillance data but no reliable data on RDT consumption (**SECTION 2.1.3**), or
- reliable data from malaria surveillance and reliable data on RDT consumption (**SECTION 2.1.4**).

QUANTIFICATION AND FORECASTING

Quantification and forecasting are the most critical aspects of procurement and require a multidisciplinary, multi-stakeholder team that overlaps with the related deployment and use of artemisinin-based combination therapies. The team should be guided by information from a logistics management and information system.

2.1.1 *Areas with no malaria surveillance data*

The estimation of requirements should be based on implementation capacity and programme aspects, i.e. the number of persons performing the RDTs, the number of tests expected to be per-

formed per day and the number of working days during which the tests will be performed. To this estimate a further proportion of RDTs should be added in order to establish a safety stock.

SAFETY STOCKS

As it is impossible to estimate requirements with complete accuracy and to be certain about the supplier's performance, a certain stock (inventory) of RDTs is needed to absorb fluctuations in supply and demand and to reduce the risk for stock-outs. As high stock levels increase inventory costs (personnel, storage, risks for spoilage, expiry and theft), most public supply systems should calculate a minimum 'safety stock'.

EXAMPLE

For example, if RDTs are to be introduced as part of a new programme for home-based management of malaria, the requirements should be calculated on the basis of the expected number of suspected malaria cases that will be tested by community health workers enrolled and trained in the programme. If the programme involves 200 community health workers, who are expected to test on average five febrile patients per day and will be working 300 days/year, the 1-year RDT requirement will be:

200 community health workers x 5 suspected malaria cases x 300 days = 300 000 RDTs per year

If the requirement for safety stocks at multiple levels is estimated to be 20% of the expected consumption, the total requirement will be:

$300\,000 \times 1.20 = 360\,000$ RDTs per year

2.1.2 Areas with unreliable malaria surveillance data

This situation is common and may be the prevalent situation in many countries. Poor reliability may be due to general underreporting or may be specific to certain health facilities, often in under-served geographical areas. In situations in which routine malaria microscopy is of poor quality, the positivity rate is unreliable. The scale-up of RDTs is expected to improve malaria surveillance in many countries, diminishing the problem of poor malaria surveillance data over time.

➔ *Whenever possible, quantification should be based on data from parts of the country with reliable surveillance data, similar malaria transmission and a similar health care system. In countries with large supplies of artemisinin-based combination therapies in public health facilities and reliable data on consumption of therapies for the period preceding the use of RDTs, data on the consumption of these drugs can be used as an additional indication of the number of patients with suspected malaria seeking treatment. In general, however, in countries or areas with unreliable malaria surveillance systems the logistics management information system is not functioning well and data on consumption of artemisinin-based combination therapies are often not available.*

For these areas, the method described below should be applied, with full recognition of the limitations of making extrapolations from different areas. The main differences that may influence the estimates and that should be taken into account are:

- differences in the number of health facilities and their functioning, which affect patient flow at different levels of the health care system,
- expected variations in patient treatment-seeking behaviour after introduction of the new malaria treatment policy, or differences in pricing of medicines and diagnostic testing, and
- different extents of deployment of malaria diagnostic services to peripheral health care facilities.

EXAMPLE

For example, if the RDT implementation plan includes peripheral health posts that did not initially have RDTs, the requirement should be increased by the proportion of patients with suspected malaria expected to seek care at health posts. If 20% of the suspected cases are treated at health posts, the overall RDT requirement should be initially increased by 20% for the period in which RDTs will be deployed at this level. The amount should then be increased by the proportion of RDTs required to constitute safety stocks at health post level.

2.1.3 Areas with reliable malaria surveillance but no reliable data on RDT consumption

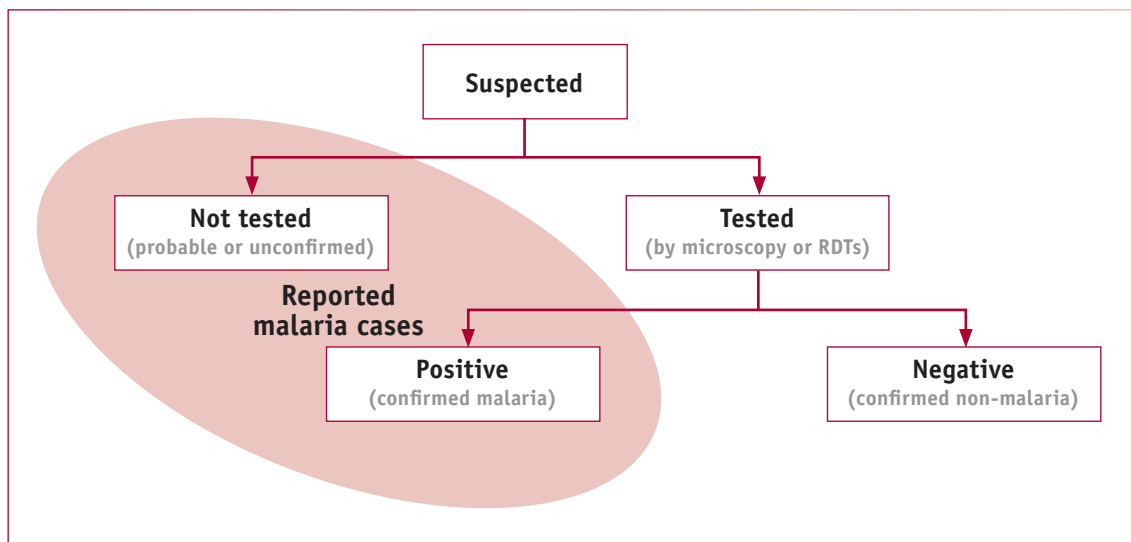
The critical variable to be obtained from surveillance data is the number of malaria cases that were *not tested* (*probable or unconfirmed*), which is generally not reported as such. This information can, however, be derived from other data recorded in the health information system. The malaria reporting system always records the following data, in places where RDTs are already in use:

- the total number of *reported malaria* cases,
- the number of malaria cases confirmed by microscopy,
- the total number of slides examined by microscopy for malaria,
- the number of malaria cases confirmed by RDT, and
- the total number of malaria RDTs performed.

In order to quantify RDT requirements, it is necessary to do some calculations with this recorded surveillance data. The relationships among these parameters are illustrated in **FIGURE 3**.

FIGURE 3

Relations between suspected cases that were tested (by microscopy and RDTs) and not tested (probable or unconfirmed) for malaria



As shown in the shaded area of the figure, the total number of *reported malaria cases* is the sum of the number of *positive (confirmed malaria)* cases plus the number of malaria cases *not tested (probable or unconfirmed)*.

To quantify the total estimate of RDT requirements, a two-step approach is required:

1. Calculate the number of malaria cases that were *not tested* (probable or unconfirmed):

The number of *not tested* (probable or unconfirmed) cases of malaria can be derived by subtracting the number of *positive* (confirmed malaria) cases from the total number of *reported malaria cases*.

Not tested (probable or unconfirmed) = reported malaria cases – positive (confirmed malaria)

Positive (confirmed malaria) = cases confirmed by microscopy + cases confirmed by RDTs

2. Estimate RDT requirements:

The total estimate of RDT requirements can then be derived from the number of *not tested* (probable or unconfirmed) cases reported as malaria plus the number of *cases tested by RDTs*; this needs to be adjusted for completeness of reporting. To this amount the requirements for safety stocks (SS) need to be added.

$$\text{RDT requirements} = \frac{\text{not tested + tested (by RDT)}}{\text{adjusted for completeness of reporting}} + \text{SS}$$

The correction for completeness of reporting, i.e. dividing by the proportion of complete reports received in time, allows a more correct estimate of the RDT requirements by taking into account the efficiency of the malaria case reporting system.

In the absence of consumption data to calculate the minimum safety stocks, it may be useful to assume that a certain proportion (e.g. 20%) of total annual RDTs requirements should always be in stock at central, provincial, district and health care facility levels. The total RDTs required (expected consumption + safety stock requirements) will then be distributed to the various health facilities proportionally to the fraction of suspected malaria cases seen at each level, taking into account the physical size of stores, the frequency of supply at each level and temperature under storage conditions.

- ***This method for estimating RDT requirements is reliable if the proportion of negative (confirmed non-malaria) cases treated and reported as malaria is low. If this proportion is high, the quantities estimated with this method should be adjusted to avoid overestimation of RDT requirement.***
- ***This approach is based on the assumption that the number of slides taken for malaria microscopy, in the health facilities that contribute to the malaria reporting system, does not vary over time. If this is not the case, the estimates should take into account plans for expansion or redistribution of malaria microscopy services.***

2.1.4 Areas with reliable malaria surveillance and RDT consumption data

The most reliable methods for estimating RDT requirements are based on actual consumption data, which depend on a functioning logistics management information system. Consumption data should be adjusted by the number of days of stock-outs, recorded on the stock record forms of the health facilities reporting consumption data.

- ***Adjusted consumption is used to calculate the minimal safety stock, which can be calculated by multiplying the consumption figures by the lead time (period between order and receipt of goods in the warehouse). Consumption and lead time should be expressed in the same unit of time, generally months.***

As data on consumption are generally not available for all health facilities, it may be appropriate to estimate the requirements on the basis of a representative sample of health facilities with reliable data on consumption and then estimate the total requirements by extrapolation.

If needs are calculated for periods of less than 1 year, e.g. 6 months or quarterly, the RDT requirements should be adjusted by taking into account changes in the seasonality of malaria transmission, which can affect the number of suspected malaria cases tested with RDTs.

EXAMPLE

If 60% of patients with suspected malaria who seek treatment are seen over the 4-month period corresponding to the malaria transmission season and RDTs are delivered twice a year, the total annual needs should be split as follows: 70% to be delivered before the malaria transmission semester and 30% after the malaria transmission period.

Countries in which RDTs have already been deployed generally have existing stocks (inventory) and stocks on order (for which firm orders have been placed, with expected delivery dates). In order to calculate 're-orders' (new orders), the existing stocks (inventory) and stocks on order should be subtracted from total needs based on expected consumption and safety stock re-order. Examples of calculations of monthly consumption from stock record forms and formulas for calculating safety stocks and quantities for re-ordering are given in **ANNEX 5**.

2.2 Transforming estimated needs into orders

Once the total requirements have been defined, and the product specifications have been agreed, the estimated requirements should be transformed into actual orders, in the following steps:

1. Estimate the requirements to fill the supply pipeline on the basis of the number of supply points at each level, their frequency of requisition and delivery and the safety stocks at each level, in line with the overall plan for distribution of RDTs.
2. Consider the effect of lead time, including the whole procurement process with time to place an order, production time, (pre-shipment) lot testing, shipment, customs clearance and arrival at the central warehouse.
3. Adjust the amounts on the basis of expected damage, spoilage, invalid tests, expiration and theft, e.g. 10%, and allow for the estimated losses in quantifying requirements. Anecdotal evidence indicates that losses can be as high as 10%. One of the objectives of the quality assurance system should be to determine the actual figure and to reduce it continually.
4. The quantity of the order should then be adjusted according to pack size (e.g. multiples of 25, 30 or 50 test units) and minimal order size.
5. Estimate total procurement costs on the basis of prices from local suppliers and international procurement agencies, adding freight and insurance costs.
6. Reduce the estimated quantities to conform to the budget, as necessary.

FURTHER READING

- Lean Procurement™. Website of Consumers Interstate Corporation, 2008.
<http://www.leanProcurement.com>
- Cavinato J, Flynn AE, Kauffman RG. *The supply management handbook*, 7th Ed. New York, McGraw-Hill, 2006.

STEP 3

Budgeting and budget components

The first component of a budget for RDT procurement is based on the quantities required over time. These quantities should be derived on the basis of a good understanding of the factors that might affect the requirements. The budget should be based on the concept of ‘total cost of acquisition’, including not only the cost of goods but all anticipated costs, from purchase to disposal. The initial full purchase price (including transport and insurance costs) is inflated by all other costs expected to be incurred, including operating expenses (distribution, supply management, information and communication, training, supervision, quality assurance and quality control, monitoring, reporting).

The budget headings and the relative size of each element should be in line with national and local or clinic-based phases of the implementation plan. The budget headings should include:

- transport and storage,
- procurement,
- purchase of RDTs,
- purchase of ancillary items and safe disposal materials,
- quality control by lot testing and laboratory monitoring,
- supply chain management,
- training and supervision,
- community education, and
- quality assurance.

Transport and storage costs, including the cost of controlled storage at other (lower) than ambient temperatures, are generally significant and can determine the feasibility of acquisition. The ancillary items and safe disposal materials comprise both test items that are not in the ‘point of care’ kit and ‘indirect’ costs such as for gloves and sharps containers (see **SECTION 4.3**). Quality control by lot testing and laboratory monitoring is presently free but may in the future become an active budget item. The budget should cover the development of a quality assurance system based on *A model quality assurance system for procurement agencies* (3).

The budget should also cover aspects of the logistics supply system that need strengthening, as a well-functioning logistics system is necessary to ensure a dependable supply of RDTs.

Sources of funds are important, as compliance with the procurement procedures varies by source of funding, and the proportions of funds allocated for RDT procurement may vary according to budget lines and funding cycles.

➔ ***An RDT programme is not a vertical or stand-alone activity. Malaria diagnosis and treatment and the related commodities are part of primary care in malaria-endemic countries, and the systems and agents that procure RDTs probably procure all the other commodities as well. The requirements for RDTs should be considered within the wider health care procurement scheme of the country.***

3.1 National funding

In most malaria-endemic countries, the contribution of the government budget to funding the procurement and use of malaria RDTs is smaller than that from external agencies. In most countries, the government budget is the main source of funding for the public health system, mainly for recurrent expenses, such as personnel costs and infrastructure. In more advanced stages of malaria elimination, most operations, including support for malaria diagnostic services, are based almost entirely on reliable domestic government spending.

3.2 Funding from external agencies

The main sources of funding for procurement of malaria RDTs for the non-profit health sector are:

- the Global Fund, which in 2010 was the source of approximately 70% of funding for malaria control in endemic countries. In rounds 4–9, the Global Fund allocated US\$ 446 million for malaria RDT procurement (more and more malaria grants have a budget for RDTs, from 54% in round 4 to 82% in round 9),
- the United States President's Malaria Initiative (15) of the United States Agency for International Development, and
- the World Bank (16).

Many funders provide guidance for application. For example, for round 10 of applications to the Global Fund, a budgeting spreadsheet (17) and a guide to its use (17) were provided. Use of such guidance is generally a requirement of application.

FURTHER READING

- *Supply Chain Excellence Total Acquisition cost*
<http://www.supplychainexcellence.co.uk/totalacquisitioncosts.htm>
 Search: "Total acquisition cost"
 - *A model quality assurance system for procurement agencies*. Geneva, World Health Organization, 2007 (WHO/PSM/PAR/2007.3).
<http://www.who.int/medicines/publications/ModelQualityAssurance.pdf>
 Search: "model quality assurance procurement"
-

STEP 4

Defining technical specifications

A specification is a detailed, unambiguous statement of the buyer's requirements in terms of the attributes and features of the product, with a description of the means by which compliance with those requirements can be verified. The specification may comprise a conformity section (or specification) and a performance section (or specification). Similarly, they may be presented in different versions: incorporating or focusing on all aspects of presentation, packaging, labelling and conditions of storage and delivery; or a more restricted, targeted technical specification comprising all aspects of safe and effective use. The specification is generally attached to the bidding documents and, consequently, forms part of the supply contract.

Once the broad criteria for RDT selection have been agreed (**STEP 1**), the individual elements should be specified to ensure safe procurement and deployment. For example, kit sizes may vary according to the point of use, e.g. village or district level. Unless care is taken, small differences can have significant unintended consequences that can jeopardize the success of a programme.

4.1 Target malaria parasite species

The RDTs currently on the market are designed to target the following parasites: *P. falciparum* (Pf), *P. vivax* (Pv), *P. malariae* (Pm) and *P. ovale* (Po), all of them (pan) or only the non-falciparum malaria species (Pvom: *P. vivax*, *P. ovale* and *P. malariae*), in the following combinations: Pf only, Pf/pan, Pf/Pv, Pf/Pvom, Pf/pan/Pv, Pv only and pan only.

4.2 Target antigens

RDTs detect malaria parasites with antibodies that target specific antigens produced by each species (**SECTION 1.1**). The target antigens detected by the malaria RDTs currently on the market are:

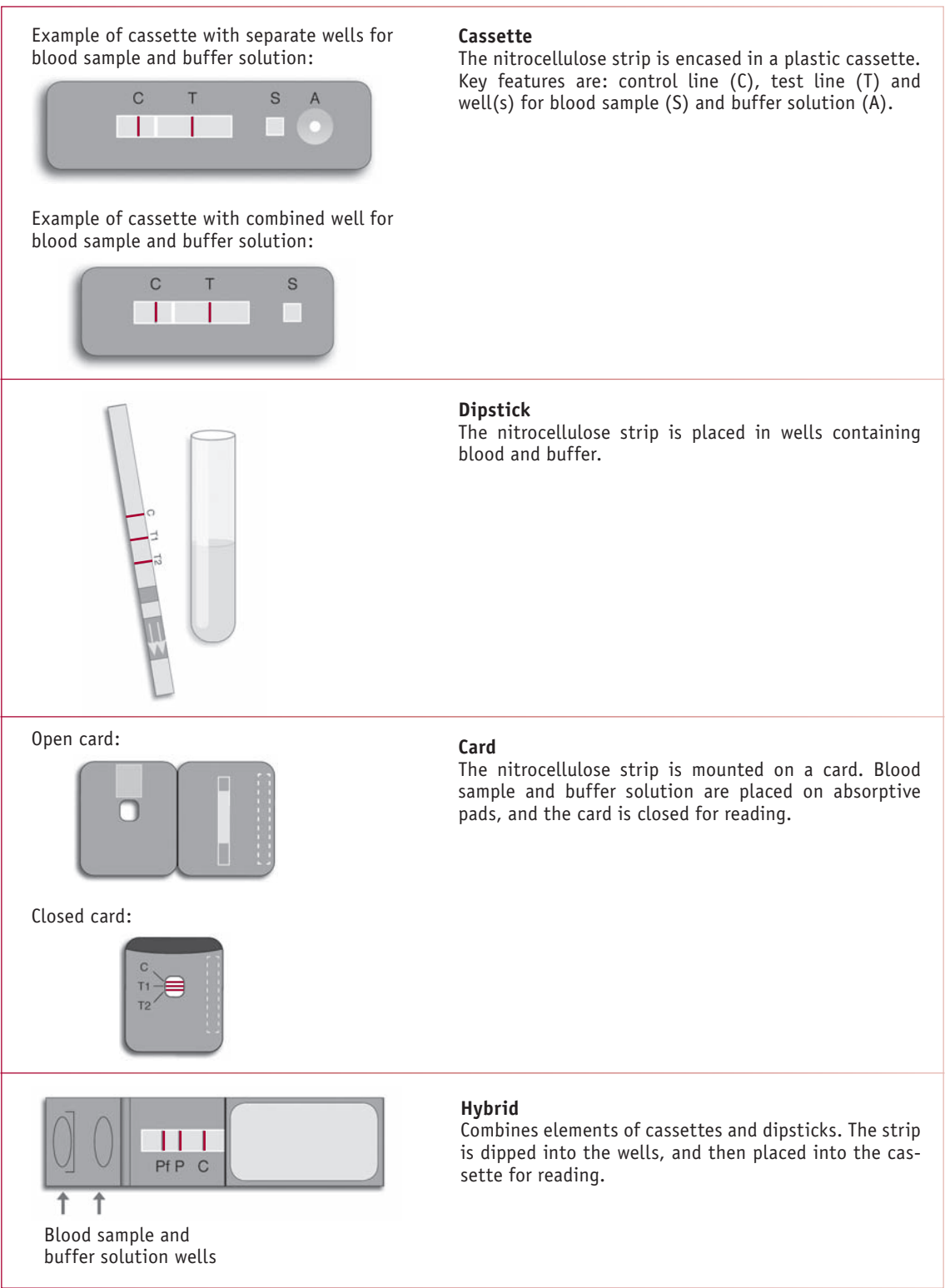
- histidine rich protein-2 (HRP2),
- *Plasmodium* lactate dehydrogenase specific for *P. falciparum* (pLDH-Pf),
- *Plasmodium* lactate dehydrogenase common to all species (pLDH-pan),
- *Plasmodium* lactate dehydrogenase specific for *P. vivax* (pLDH-Pv),
- *Plasmodium* lactate dehydrogenase specific for *P. vivax*, *P. ovale* and *P. malariae* (pLDH-Pvom), and
- aldolase.

4.3 Format and ancillary items

4.3.1 Components of an RDT kit

RDTs commonly come in four different formats: Cassette, dipstick, card, or hybrid formats which combine different elements of them. Examples are shown in **FIGURE 4**.

FIGURE 4
Examples of different formats of RDT



It should be noted that tubes are not always provided with dipsticks, and the procurement management team should cover this requirement in the tender. The requirements for ancillary items differ for the different formats of RDT, and this can affect the procurement programme and budget. Changes in format can also have consequences for training and other management aspects.

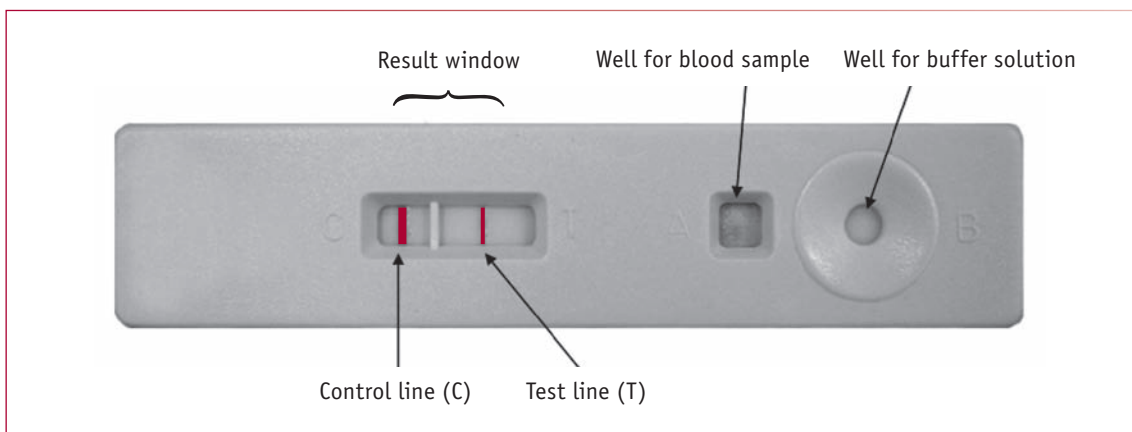
On the basis of results and experience, users prefer cassettes because of the ease and simplicity of use, fewer steps in their use and better performance. RDT performance should be the first criterion, and the format should be selected on the basis of ease of use.

The components of the cassette format are (**FIGURE 5**):

- a plastic case,
- a test strip, comprising the nitrocellulose strip and the materials bound to it (inside the cartridge),
- a sample well (into which blood is transferred),
- a buffer well (into which drops of buffer solution are placed), and
- a 'results window' (in which test and control lines appear).

In some RDTs, one well is used for both the sample and the buffer.

FIGURE 5
Schematic representation of an RDT cassette



Although cassettes and cards tend to be more expensive, they are simpler to use, require less training, particularly of minimally trained, non-laboratory users in remote locations, are cleaner and safer and may require fewer ancillary materials (e.g. tubes).

When RDTs are specified as 'point of care tests', ancillary items are provided, packaged as indicated. Otherwise, they must be acquired separately and packaged as shown. They include:

- a sterile lancet (in the box),
- a blood collection device (in the box or pouch),
- a buffer bottle and dropper (in the box or pouch),
- an alcohol swab (in the box), and
- appropriate desiccants, if specified. The absence of desiccant from a manufacturer's specification and product is not a deficiency, as specific RDTs may not require a desiccant.

Gloves and safe disposal kits (e.g. sharps boxes) are bought and provided separately. Clocks (watches, mobile phones) are generally already available in health facilities. Minimum–maximum thermometers may be required for monitoring storage temperature.

The dipstick format requires a well or tube for mixing blood and buffer, into which the immuno-chromatographic nitrocellulose test strip is dipped. This facility is built in in the two other forms, card and cassette.

4.3.2 Format of RDT cartridge

The cassette format consists of a test strip encased in protective plastic housing, with wells for adding sample and buffer and a result-viewing window. The test strip is made of nitrocellulose membrane embedded with antibodies, an indicator pad and an absorption pad. **FIGURE 5** shows typical conformations of the cartridges.

4.3.3 Writing space on RDTs

A writing space on the cartridge is required to record the patient's identification, date and test number. There is always space on the front and back of the cassettes or on the front of the cards.

4.3.4 Labelling of lines

Cartridges have a single control line but one or more (up to three) test lines, depending on the RDT. The exact labelling of the lines should be defined and recorded in the technical specifications. While the control line is usually labelled 'C', when space permits, the test line for *P. falciparum* may be labelled 'Pf', that for *P. vivax* as 'Pv', that for non-falciparum as 'non-Pf' and that for pan-malaria antigens as 'pan'. For tests that detect multiple antigens, the correct labelling of the lines is important to ensure clear interpretation of the results.

Sometimes, test lines are labelled 'T1', 'T2' and 'T3' (counting from the 'C' line), depending on how many antigens or combinations are being detected. Common types and sequences of C and T lines are shown in **ANNEX 6**.

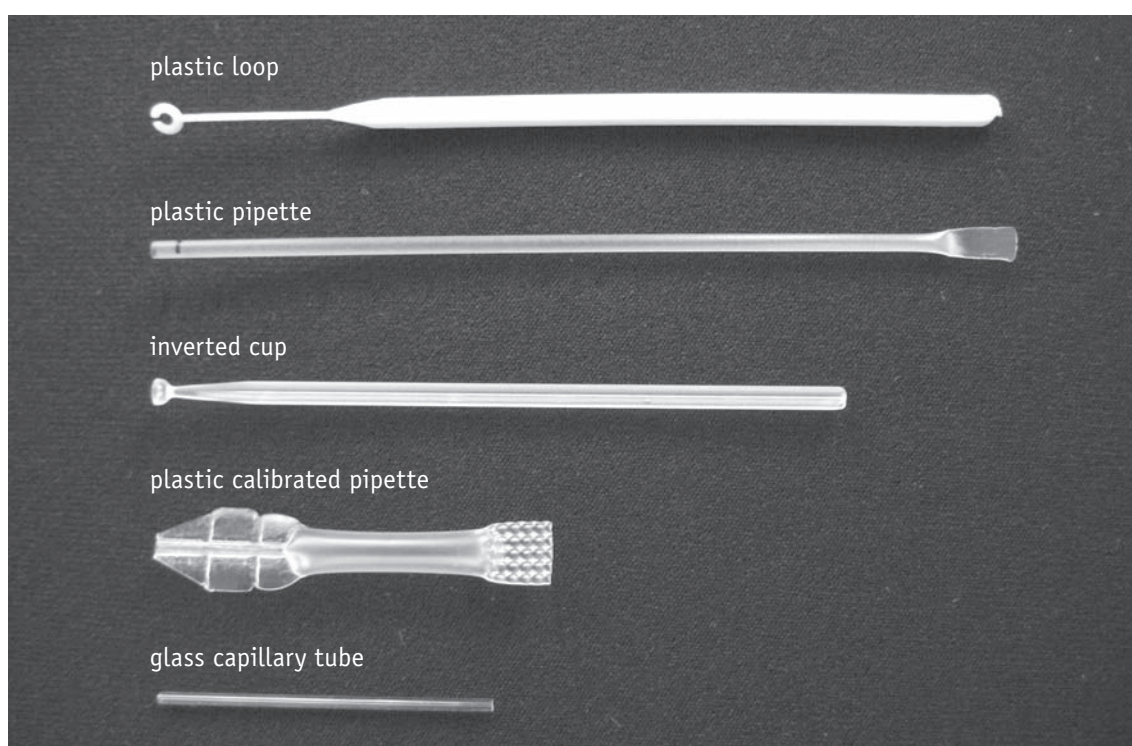
4.3.5 Blood transfer devices

Blood collection transfer devices (18) are used to transfer the blood sample from the patient (or previously collected) to the RDT. Consistency, accuracy of blood volume, blood safety and ease of use are critical to safe, accurate RDT performance. A variety of devices are available, including straws, inverted cups, loops, pipettes and capillary tubes, some of which are illustrated in **FIGURE 6**. A recent study¹ showed that the performance of blood transfer devices varied in accuracy, blood safety, ease of use, and user preference. In this evaluation, the inverted cup design achieved the highest overall performance, while the loop also performed well. Switching between devices is likely to require retraining of health workers, printing of job aids and related materials as well as a requirement to procure new collection transfer devices. It should therefore not be undertaken lightly.

The type of device for collecting blood that is supplied as part of a 'point of care' kit is specified by the manufacturer. Glass capillary tubes, although available and specified for RDTs, are costly, breakable and raise safety concerns. Sometimes options are provided, and manufacturers may respond positively to a request for a specific device; however, as the device for collecting blood is not considered to affect the performance of the RDT, specifying a nonstandard option may affect its price. The type of blood transfer device should be reflected in the product coding.

¹ Hopkins et al. Blood transfer devices for malaria rapid diagnostic tests: evaluation of accuracy, safety and ease of use. *Malaria Journal*, 2011, 10:30.

FIGURE 6
Blood collection transfer devices



Source: Heidi Hopkins, FIND

4.3.6 Dispenser of buffer solution

The dispenser varies from single to multiple use, depending on whether it is for a single RDT (and packaged with the test) or for multiple or single tests and contained in a bottle in the secondary packaging. Single-use droppers are provided by some manufacturers; although the cost may be higher, single-use dispensers may be preferable in settings in which few tests are performed.

It is critical to use the buffer supplied, as opposed to other liquids. Buffer solutions are not interchangeable for lots of the same product, for products from the same manufacturer or for products from different manufacturers.

4.4 Diagnostic performance

The rationale for basing procurement decisions on diagnostic performance in WHO product testing is stated in **SECTION 1.2**. At present, data from rounds 1 and 2 are available for 68 malaria RDTs currently on the market (1). It is important to establish the unique identity (product code) of the product being procured and be certain that it corresponds to its test results.

Diagnostic performance is assessed from:

- a panel detection score of 200 parasites per microlitre against panels of *P. falciparum* and *P. vivax* (**SECTION 4.4.1**),
- the false-positive rate (**SECTION 4.4.2**), and
- the invalid rate (**SECTION 4.4.3**).

In addition, WHO product testing for malaria RDTs includes systematic evaluation of thermal

stability for 2 months at 35 °C and 45 °C (SECTION 4.4.4) and ease of use (procedural steps, kit completeness and interpretation, SECTION 4.4.5). The product specifications may indicate threshold levels for the above parameters to be supplied by the applicant.

➔ *The threshold levels recommended by WHO are given in SECTION 1.3.1.*

4.4.1 Panel detection score against panel at low parasite density

The ‘panel detection score’, previously called the ‘detection rate’ (12), at a low density (200 parasites per microlitre) of panels of wild-type *P. falciparum* and *P. vivax* is the main parameter that differentiates the malaria RDTs in terms of diagnostic performance. While the panel detection score is not equivalent to diagnostic sensitivity, the score at 200 parasites per microlitre provides an indication of which products are likely to be more sensitive in the field, particularly in populations with low-density infections.

4.4.2 False-positive rate

The total false-positive rate is the sum of two rates that measure lack of specificity: the proportion of incorrect species identification, and the proportion of positive results for samples containing no *Plasmodium* spp. parasites (1). In WHO product testing, false-positive results are measured as the percentage of all RDTs that incorrectly gave a positive result, on the basis of the manufacturer’s minimum reading time.

4.4.3 Invalid rate

The ‘invalid rate’ is the frequency with which an RDT fails to develop a control line when tested against the parasite-positive panel (1).

4.4.4 Heat (thermal) stability

In this evaluation, RDTs are incubated for 2 months at 35 °C and 45 °C and then retested to evaluate their performance at these temperatures. The importance of the thermal stability of an RDT varies with the ambient conditions under which it is expected to be transported and stored. Thus, stability at high temperatures is vital if an RDT is to be stored in clinics in a country in which the ambient temperature can reach 45 °C, but it is less critical at high altitudes or in cooler tropical environments where the temperature rarely rises above 35 °C.

It is important to consider the implications of these requirements for maintaining RDT product quality throughout the supply chain, particularly during steps such as transport to the country of receipt, trans-shipment and customs clearance, when the risk may be greatest. Control measures might include both preventive steps to avoid undue delays and the use of temperature-monitoring devices (SECTION 10.1).

➔ *Most manufacturers recommend storage and distribution at temperatures between 2 °C and 28–45 °C. Freezing may destroy diagnostic performance, and exposure to temperatures above the range specified by the manufacturer may accelerate degradation of the RDT, affecting the reliability of the test and reducing its diagnostic performance, especially at low parasite densities.*

4.4.5 Ease of use description

Ease of use is evaluated by the technicians who used the RDTs in product testing. It covers:

- blood transfer device characteristics, which are important for the safety of the user and the accuracy of the volume to be transferred,
- number of testing steps required,
- total time required to obtain a result, and
- additional information: format, simplicity, clarity of results, items included in the package and language of the instructions.

These characteristics supply a minimal but valuable set of parameters for comparing the time requirements and the relative complexity of performing the RDTs.

4.4.6 Use of the FIND web-based interactive product selection guide

The FIND web-based interactive guide (FIGURE 7; 10) is the most direct means for reviewing the results of rounds 1 and 2 WHO product testing of malaria RDTs on all performance criteria, including thermal stability. Use of the guide allows selection of RDTs that match different procurement performance requirements.

The interface provides 'sliders' for each numerical entry (FIGURE 7). After choosing the corresponding selection criteria (FIGURE 8) and clicking on the 'Display/Refresh' button, the tested RDTs meeting the entered criteria are displayed, either in table format or as a graph (FIGURE 9).

➔ **The FIND web-based interactive guide helps users to select RDTs that have been evaluated in the WHO testing programme according to the parameters listed in SECTIONS 1.2. and 1.3.**

FIGURE 7
FIND interactive guide for malaria RDT product testing

FIND
foundation
for innovative new diagnostics

HOME PAGE - FIND Malaria Program

Malaria RDT product testing: interactive guide

This interactive guide is designed to help select malaria RDTs with the specific performance characteristics required by national malaria control programmes, based on the results of the WHO-FIND malaria RDT product testing programme Round 1 (2008) and Round 2 (2009).

Set parameters:

Select target malaria species: All species

Minimum panel detection score for *P. falciparum* (%): [slider]

Minimum panel detection score for *P. vivax* (%): [slider]

Maximum false positive rate: [slider]

Maximum invalid test rate: [slider]

Test format: Any

Choose data to display:

☒ Panel detection score, 200 parasites/µl

☐ Panel detection score, 2000-5000 parasites/µl

☐ Invalid rate

☐ False positive rate

☐ Heat stability, 200 parasites/µl

☐ Heat stability, 2000 parasites/µl

Display / Refresh

Change / Hide

Adapted from: http://www.finddiagnostics.org/programs/malaria/find_activities/product_testing/malaria-rdt-product-testing/

FIGURE 8
FIND interactive guide: entry of selection criteria

FIND
 foundation
 for innovative new diagnostics

Malaria RDT product testing: interactive guide

This interactive guide is designed to help select malaria RDTs with the specific performance characteristics required by national malaria control programmes, based on the results of the WHO-FIND malaria RDT product testing programme Round 1 (2008) and Round 2 (2009).

HOME PAGE - FIND Malaria Program

Set parameters:

Select target malaria species: All species

Minimum panel detection score for *P. falciparum* (%): 75

Minimum panel detection score for *P. vivax* (%): 75

Maximum false positive rate: 10

Maximum invalid test rate: 5

Test format: Any

Choose data to display:

☒ Panel detection score, 200 parasites/µl

☐ Panel detection score, 2000-5000 parasites/µl

☐ Invalid rate

☐ False positive rate

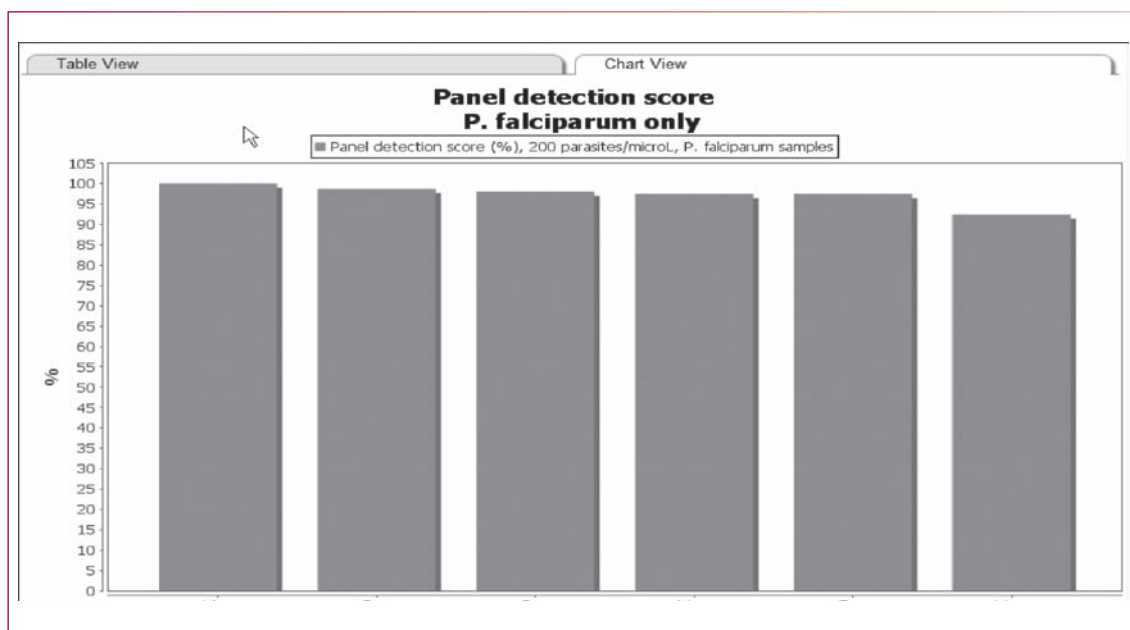
☐ Heat stability, 200 parasites/µl

☐ Heat stability, 2000 parasites/µl

Display / Refresh

Adapted from: http://www.finddiagnostics.org/programs/malaria/find_activities/product_testing/malaria-rdt-product-testing/

FIGURE 9
FIND interactive guide: results in chart view



Adapted from: http://www.finddiagnostics.org/programs/malaria/find_activities/product_testing/malaria-rdt-product-testing/

4.5 Sensitivity and specificity

In principle, the product specifications included in tenders should not make reference only to a required level of diagnostic sensitivity and specificity but should also specify the required panel detection score, false-positive rate and invalid rate (see limitations of sensitivity and specificity in SECTION 1.2.2).

4.6 Stability of results

Test and control lines may fade and change in intensity over time and fade at different rates. This varies by manufacturer, but all lines generally stay for few days. The procurement management team should ensure that the manufacturer defines the ‘reading window’ (the appropriate time after execution that the test should be read) for the assay and that this is prominently displayed on the product label and information.

4.7 Declared reading time

The ‘declared reading time’ is the time from adding the blood and drops of buffer solution to reading the test results. For all malaria RDTs, the minimum time to results is indicated in the product leaflet and may vary according to the product (e.g. 15, 20 or 30 min). Some manufacturers may also indicate the maximum reading time (e.g. 20 or 30 min, with a minimum reading time of 15 min). For most products there is a recommended reading time, which is preferably a range, as it is not possible to read an RDT consistently at an exact moment, provided the results are stable during the reading time. It is important to adhere to the reading time (1).

4.8 Shelf-life

The shelf-life is the duration after manufacture in which the RDT may be used and is specified on the RDT as the ‘latest use date’. The procurement specification and tender may specify a minimum shelf-life on delivery. The procurement team should consider the effect of transport times on residual shelf-life, including the time required for transport from the port of receipt to the point of storage for use.

4.9 Packaging and kit contents

Packaging covers the range of containers, from the sealed impermeable packet to the outer transit container and any container specifically allocated for storage of the device and ancillary items. The levels of packaging are usually described as *primary packaging*, which consists of individual sealed foil pouch containing individual RDTs, and *secondary packaging*, which is a unit box containing a defined number of tests. Malaria RDTs are sensitive not only to temperature but also to humidity, which weakens the bonds between the antibodies and the control and test bands, and should therefore be packaged to ensure adequate protection from humidity and other contaminants, from the manufacturing plant through transport, storage and the entire shelf-life, up to the moment of use. Sealed, impermeable foil pouches are therefore generally supplied with desiccant, such as silica gel.

➔ ***Preference should be given to desiccants with a colour indicator of humidity. It is the responsibility of the manufacturer to provide accurate information on the properties, safety hazards, remedies and safe disposal of any such desiccants.***

The other requirements of the kit content, such as the number and type of blood transfer devices, sterile lancets and alcohol swabs, should also be indicated in this section of the technical specifica-

tions. The packaging specification should be sufficiently detailed to ensure that the manufacturer provides integrity of sealing, with no weaknesses in the sealed areas of the pouch that permit leaks during normal handling, which could adversely affect the quality and performance of the RDT. Commonly used physical tests for package integrity and seal include visual inspection, a bubble test and a vacuum leak test. The choice of method is the prerogative of the manufacturer; however, manufacturers should be required to submit documentary evidence that their products have undergone and passed an appropriate, validated packaging test before release by the quality assurance department of their company.

4.10 Labelling

The essential information that must be clearly visible on the primary and secondary packaging includes:

- product name,
- product description,
- catalogue number (product code),
- date of manufacture, in order to calculate the percentage of shelf-life at any given date,
- expiry date,
- lot number: usually defined as a production run with a particular batch of monoclonal antibodies and nitrocellulose strip, normally defined by a batch number, typically consisting of 40 000–80 000 RDTs,
- recommended storage temperature and requirements, and
- manufacturer, with contact details.

Ideally, the labelling should also clearly specify the indication for the test (e.g. ‘malaria test’). The name of the manufacturer and manufacturing site should be stated. Language requirements may be also included, and key information in the language of the country of use should be provided. The requirements for labelling of the European Commission Directive on in vitro diagnostic devices (19) and the Global Harmonization Task Force (20) are given in **ANNEX 7**.

4.11 Product information for users (package insert)

Information on how to use the device safely and properly in the language(s) (both national and regional, if necessary) of the country of use is required in each unit pack, for example in each box containing a multiple of 25–60 RDTs. The information in the package insert should include:

- how the test works, including reference to the RDT as ‘immunochromatographic’ and what this means for test use,
- how the test is done, with all the steps involved, and
- interpretation of the results (usually with a pictogram).

The package insert should also cover:

- recommendations for storage of the device, which should come first in the instructions, so that the integrity of the device is not compromised before it can be used,
- a list of contents and instructions to check that each item is present,
- drawings illustrating the explanations, with use of colour, which sharpens memory and improves device use,

- the target antigens and malaria species that the test can identify,
- instructions on the safe use of all ancillary items, such as the lancet, the blood collection transfer device and gloves, and on blood safety procedures, including safe disposal of used lancets and test devices,
- reading time, indicating poor reliability if the test results are read after the recommended time, and
- a statement that the test cannot be used to investigate treatment failures after antimalarial treatment, as antigens may persist for a few weeks after elimination of the parasite from the blood (see **ANNEX 1**).

The requirements for product information of the European Commission Directive on in vitro diagnostic devices (19) and the Global Harmonization Task Force (20) are given in **ANNEX 7**.

FURTHER READING

- *Malaria RDT product testing: interactive guide*. Geneva, Foundation for Innovative New Diagnostics.
http://www.finddiagnostics.org/programs/malaria/find_activities/product_testing/malaria-rdt-product-testing/
Search: “**malaria RDT product testing: interactive guide**”
 - *European directive on in vitro diagnostic medical devices (98/79/ec) – QSOP 33, Issue 4.1*. Health Protection Agency (2008).
<http://www.hpa-standardmethods.org.uk/documents/qsop/pdf/qsop33.pdf>
Search: “**europaean directive diagnostic medical devices**”
 - International Organization for Standardization. *ISO 11607:2006 Packaging for terminally sterilized medical devices – Part 1: Requirements for materials, sterile barrier systems and packaging systems. Part 2: Validation requirements for forming, sealing and assembly processes*. Geneva.
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STEP 5

Procurement method and tender documents

STEP 5

5.1 Procurement method

The aim of procurement is to secure the lowest possible purchase price for quality-assured products, to ensure the reliability of suppliers in terms of both quality and service, to maintain transparency and to minimize opportunities for illicit influences on procurement. Funders may have their own nomenclature for bidding, e.g. ‘international bid’ and ‘limited international bid’, with correspondingly open or limited tenders. Four procurement methods can be distinguished (4):

- *Open tender*: Any supplier can submit an offer. As in vitro diagnostic medical devices such as malaria RDTs must meet complex quality criteria, which should be assessed before the procurement cycle (see **STEP 4**), open tenders are not recommended for their procurement.
- *Restricted tender*: Only prequalified suppliers can submit offers. As described in **SECTION 1.2.1**, confirmation of performance in WHO product testing is at present a suitable criterion for restricted tenders.
- *Competitive negotiation*: The buyer approaches a limited number of suppliers that meet some predefined criteria and bargains directly with them to achieve specific price and service arrangements. This method may be suitable for items that are not widely available, for small volumes or low-value items or for emergency purchases to supplement tenders.
- *Direct procurement*: Purchase is made directly from a single supplier at the quoted price. This option is not ideal, as dependence on a single supplier may not guarantee a sustained supply of products at affordable prices in the long term.

The procurement method depends on the requirements of the funders and also on any national procurement policies and guidelines.

To avoid dependence on a single supplier, some procurement entities award a bid for a proportion of the required quantities to two or more suppliers. Such ‘*split awards*’ systems minimize the risk for supplier default but are likely to raise prices and require careful management, as separate procurement streams can result in acquisition of different products, with different training requirements and supply management needs.

In some countries, preference is given to local manufacturers, at least for public procurement; however, this may conflict with the procurement guidelines of the country or of the funding agencies.

Manufacturers must be able to supply RDTs that meet the requirements in the specification if they are to be considered for bidding. Procurement entities should obtain bids from several suppliers that are able to supply RDTs that meet the required specifications. Procurement requires considerable expertise and resources. Some buyers, including most national governments, have an experienced procurement unit. Those that do not should consider using an international procurement agency (21). Funding agencies might appoint a procurement agency, and procurement systems such as the ‘voluntary pooled procurement’¹ might be considered. The desirability of hav-

¹ <http://www.theglobalfund.org/EN/procurement/vpp/>

ing a sole or nominated, single source and issues of standardization and harmonization might be introduced, but the policy will have to be justified and documented before funders and national procurement bodies will accept them. Even if a sole source is requested, many funding bodies involved in procurement will require competitive bidding for procurement of RDTs.

In many cases, the procurement method of choice for procuring the RDTs is the restricted tender.

5.2 Tender documentation

Tender documentation depends on the requirements of funding and procurement agencies. In some countries, the requirement for registration is part of the documentation that must be submitted by the manufacturer. Other requirements are included in the technical specification and in the section of the tender documents that defines the commercial and logistic framework for procurement. The following aspects should be covered:

- the determinants of the required RDT (**STEP 1**),
- the technical specifications and documentation that must be submitted (**STEP 4**),
- requirements for outer packaging and shipping, which include compliance with norms, dimensions, volumes, stacking requirements, materials, crush resistance, padding and external marking,
- required quantities and delivery schedules (**STEP 2**),
- required ordering procedures, delivery terms (e.g. port of destination) and prices are directly comparable only if they are based on the same Incoterms (22),
- applicable terms and conditions that will form the basis for selection,
- time frames for submitting bids and for orders and delivery (Bidders should be alerted to any anticipated delays, for example if in vitro diagnostic devices have to be authorized for use in the destination country.),
- procedures for awarding tenders, and
- any special conditions in adjudicating tenders, such as preference for products evaluated in WHO product testing (10), prequalification, registration requirements, assessment by a stringent regulatory authority and meeting minimum levels of diagnostic performance.

Specific requirements in relation to RDT quality control should be identified in the bidding documents, such as:

- permitting a sampling agency to perform random sampling of RDTs at the manufacturing facility for lot testing (**STEP 9**),
- accepting the test results of an independent laboratory agreed to by both parties, and
- accepting the established, agreed procedure for the resolution of disputes.

Additional general and specific conditions of the contract may include:

- country of origin of the RDT,
- supply chain, source of components and site location of processes; a ‘badged’ product can extend beyond relabelling and repackaging: unless prequalification is used, in which the supply chain is fully identified, the sources of elements of the supply chain (materials, components, assembly, kit building, packing, labelling and any repacking and labelling) might have to be identified,

- request to applicants to state their administrative and legal details (see also **SECTION 7.2**), their link with the product and their commitment to ongoing quality, and
- a standardized proposal form, stating delivery lead times, expected delivery date, gross weight of the order, personnel involved and contact details, and a quotation for the total amount, including any discounts.

New manufacturers or manufacturers that the buyer is using for the first time should be required to provide documentary proof of financial capacity in the form of audited accounts (usually for the past 3 years). A record of previous supplies and a list of potential referees should also be required in the tender responses. Framework agreements specify minimum order quantity, batch size, production capacity and related product realisation issues.

Most funders have their own format for bidding documents, but this is not a universal approach. For example, the Global Fund does not have specific bidding forms, and requirements are based on principles set up in the model quality assurance system (3) and interagency guidelines for good pharmaceutical procurement, as described in the Global Fund's policies on procurement and supply management (23). Information and guidance on procurement are available on the web sites of many funding organizations

Tender documentation spells out the technical requirements and the criteria for awarding bids. The documentation is the basis for all future contracts. Subsequent changes can cause additional costs and delays and may appear unjustified to contract partners, especially if they are unexpected.

- ➔ ***Procedures must be consistent, to make the tender process fair and transparent.***
- ➔ ***Technical requirements must be well planned to minimize avoidable changes. Any anticipated adaptations (such as language or packaging requirements for specific settings of use) should be mentioned in the tender documentation.***

STEP 6

Inviting tenders

Tender invitation represents a significant portion of the procurement cycle (see **ANNEX 3**). Tenders should invite manufacturers that have been independently assessed and shown evidence of compliance with the product technical specification, for example, in WHO product testing, and evidence of capacity and competence to meet the procurement requirements. Independent assessment includes verification of claims to competence and capacity by a party other than the manufacturer: a second party is bound contractually and would, for example, include the purchaser; a third party is independent of the party being assessed, the manufacturer and any second party. The third party might be a regulatory or assessment body, such as a notified body conducting ISO 13485 certification assessments in the country or an independent organization performing prequalification. The assessment may be based on submitted documentary evidence, some of which might have been notarized (independently authenticated), or it may include on-site inspection. The assessment may have been carried out before procurement, as a requirement to be on an approved list or to be a prequalified supplier. Evidence of capacity and competence can be provided as authenticated statements of plant capacity, delivered orders, infrastructure, financial resources, staff in positions of responsibility and their background, training and performance as shown by authenticated testimonials. It should also include an authenticated statement of the effective management of the whole manufacturing operation, as is included, for example, in an authenticated certificate of assessment against ISO 13485:2003 (11). These documents are collected as part of the 'product dossier' and 'site master' files, which are submitted and assessed before a prequalification site inspection.

The independent assessment should include assessment of the diagnostic performance of the product. In addition to submitting documentation on the product and the supplier meeting the tender requirements (as outlined below; see also **STEP 7**), the tender document should also specify that the manufacturers are expected to submit free samples (e.g. 60–100 tests) of the RDTs, which will be used by national experts in RDT use and evaluation to assess ease of use, RDT components and labelling in compliance with the claims made in the product leaflet.

Pre-bid meetings with manufacturers often add information and clarify technical specifications.

6.1 WHO product testing

The results obtained in the independent performance assessment of this testing programme are critical to procurement of a well-performing diagnostic product (10). The parameters and recommended thresholds are described in **SECTIONS 1.2, 1.3 and 4.4**.

6.2 Assessment by national regulatory authorities

Diagnostic products must comply with national regulations for product registration or authorization, where these exist. Procedures for assessing conformity vary with the required level of risk assessment for the diagnostic devices. (for instance, the European Commission Directive (19) classifies devices into categories based on risk.) Regulations typically list essential requirements

for the safety and effectiveness of diagnostic devices that may complement technical product requirements. Registration or authorization of diagnostic devices by the competent national authority may be based on the work of a certification body competent in assessment of the quality of medical devices.

The procurement agent must establish whether the products require registration in the country where they are to be used, and he or she should be familiar with what constitutes product registration in the recipient country. The agent must refer to the national regulatory body of the recipient country to establish the need for product registration (24).

Care should be taken to identify the criteria under which countries can buy RDTs, the documents for importation and customs clearance required and any local or other product specifications the country might have. These preferences will require justification to be acceptable, particularly in a donor-funded or other procurement situation. A procurement body with significant international experience should be able to identify the channels, bodies and requirements in countries of interest. The registration requirements in some countries may differ according to whether the device is donated or is for the general retail market; the requirements for the latter will be more stringent.

6.3 Risk management of rapid diagnostic tests for malaria not evaluated in the WHO programme

The requirements of funding agencies and national regulatory authorities for procurement of RDTs may not include assessment of the RDT in WHO product testing. Under exceptional circumstances, such as large-scale deployment of specific RDTs and experience of health workers with products that have been assessed in different evaluation schemes, the programme requirements may justify the procurement of such RDTs. In such cases, the evaluation of the results of assessments submitted by manufacturers in published or unpublished studies (see **SECTION 6.2**; 25) might be the only information available for deciding to procure a malaria RDT that has not been evaluated in WHO product testing. Such reports vary from simple summary tables of unpublished data to peer-reviewed published papers. The methodological issues to be assessed in ensuring the validity of these study reports include:

- the parasite densities at which performance was measured and reported,
- the study protocol and validation methods used to assess performance of microscopy (often the gold standard), as well as methods used to assess competence (or accreditation), and
- the inter-lot variation in diagnostic performance.

The use of lot testing alone to assess RDTs that have not already been evaluated in malaria RDT product testing might lead to the approval of tests with poor performance. It is therefore recommended that only RDTs that have undergone full product testing be selected.

FURTHER READING

- *Principles of conformity assessment for in vitro diagnostic (IVD) medical devices*. Global Harmonization Task Force, 2008. GHTF/SG1/N046:2008.
http://www.ghtf.org/documents/sg1/sg1final_n046.pdf
Search: “principles conformity assessment in vitro diagnostic”
 - *Medical device regulations. Global overview and guiding principles*. Geneva, World Health Organization, 2003.
http://www.who.int/medical_devices/publications/en/MD_Regulations.pdf
Search: “medical device regulations”
-

STEP 7

Evaluating bids and awarding contracts

7.1 Product criteria

The committee evaluating suppliers' bidding documents should include procurement specialists and experts in the quality of diagnostic devices who have the technical expertise to evaluate the documentation and certification submitted by suppliers. The product criteria are the characteristics provided in the product specifications, identified in **STEP 4**, and attached to the bidding documents.

Validation of technical specifications can be facilitated by use of the product specification checklist in **TABLE 5**. These are example requirements, and this table may be used as a template for procurement.

The dossier requires analytical information on diagnostic performance, including sensitivity and specificity. If the results of performance in the WHO testing programme are available for the RDT, they should form a substantive element of the documentation submitted by the manufacturer.

➤ *The product specifications should be detailed in the tender documents in order to guide the manufacturer in the compilation of tender documents. The product dossier and documentation submitted by the manufacturer should comply with the WHO product dossier guidelines (26), summarized in ANNEX 8.*

Table 5. Product specifications for rapid diagnostic tests for malaria

Characteristic	Example requirement	Proof of compliance	Entity responsible for assessment
4.1 Target malaria parasite species	Specify the target parasite species or combination of species for the RDT (1.1, 4.1)	Field studies, WHO product testing programme	National malaria control programme
4.2 Target antigens	Specify the target antigens for the RDT (1.1, 4.2)	Field studies, WHO product testing programme	National malaria control programme
4.3.1 Components of an RDT kit	Format (dipstick, card, cassette or hybrid) and ancillary items (lancets, blood collection device, alcohol swabs, buffer, desiccants, gloves, safe disposal kits,...)	RDT samples including all kit components	National malaria control programme, receipt inspection (10.3)
4.3.2 Conformation of RDT cartridge	Shape, size, components of cassette cartridge	Samples of RDT cartridge	National malaria control programme, receipt inspection (10.3)
4.3.3 Writing space on RDT	Adequate space for patient name, date and RDT identification number	Samples of RDT	National malaria control programme, receipt inspection (10.3)

Table 5. Continued

Characteristic	Example requirement	Proof of compliance	Entity responsible for assessment
4.3.4 Labelling of bands	Clear labelling is important for all bands and especially multiple test bands.	Samples of RDT	National malaria control programme, receipt inspection (10.3)
4.3.5 Blood transfer device	Plastic straw, glass capillary tube, plastic loop, plastic pipette	RDT samples including all kit components	National malaria control programme, receipt inspection (10.3)
4.3.6 Dispenser of buffer solution	Single dispenser or bottle to be used for multiple RDTs	RDT samples including all kit components	National malaria control programme, receipt inspection (10.3)
4.4.1 Panel detection score at low parasite density (200 parasites/μl)	≥ 50% for Pf in areas of high transmission ≥ 75% for both Pf and Pv in areas of low to moderate transmission	Reports of the WHO product testing programme	National malaria control programme
4.4.2 False-positive rate	< 10%	Reports of the WHO product testing programme	National malaria control programme
4.4.3 Invalid rate	< 5%	Reports of the WHO product testing programme	National malaria control programme
4.4.4 Heat (thermal) stability	< 30 °C, 35 °C, 45 °C depending on conditions of intended use	Reports of the WHO product testing programme	National malaria control programme
4.4.5 Ease of use	Ease and safety of blood transfer, number and sequence of steps, timing and interpretation of results	Reports of the WHO product testing programme, and testing of samples for compliance with package insert	National malaria control programme or national research institute
4.5 Sensitivity and specificity (optional)	High sensitivity and specificity	Published field studies meeting at least the five criteria for reliability (27)	Expert review panel on malaria diagnostics and national malaria control programme
4.6 Stability of results	Stability of positive and negative results within the recommended reading time	Testing of compliance with package insert	National malaria control programme or national research institute
4.7 Declared reading time	e.g. 15, 20, 30 min as indicated in package insert	Testing of compliance with package insert	National malaria control programme or national research institute
4.8 Shelf-life	"Latest use date", residual shelf-life after receipt of goods	RDT samples	National malaria control programme, receipt inspection (10.3)
4.9 Packaging and kit contents	Primary and secondary packaging and completeness of kit contents	RDT samples	Procurement management unit and national malaria control programme, receipt inspection (10.3)
4.10 Labelling	Product name, product description, catalogue number, date of manufacture, shelf-life, expiry date, lot number, temperature storage requirements, manufacturer details	RDT samples	Procurement management unit and national malaria control programme, receipt inspection (10.3)
4.11 Product information for users (package insert)	Indications for use, procedures (including on blood safety), interpretation of results	RDT samples	Procurement management unit and national malaria control programme, receipt inspection (10.3)

7.2 Supplier criteria

The main criteria of a good supplier are competence and capacity, which are evaluated in the commercial section of the tender. A policy for supplier evaluation and selection should be established, as required in ISO 13485:2003 (11), and all suppliers (new and established) should be brought under the scope of the policy; the documentation required of new suppliers should be sought and established for existing suppliers.

➔ ***Competence is evaluated by independent assessment of the product and the technical and managerial competence of the company. For malaria RDTs, this is provided by ISO 13485:2003 certification of the manufacturer and any directly associated medical device regulatory approvals. All manufacturers that submitted RDTs for evaluation by WHO product testing have current ISO 13485:2003 certification, a standard designed to assure consistent quality of the final product if correctly implemented.***

ISO 13485:2003 requires manufacturers to assemble a technical file covering every aspect of the specification, production, processing and testing of the product. This document provides the basis and substance of the product dossier submitted for medical device prequalification (see also SECTION 7.1). ISO 13485:2003 certification is also discussed in SECTION 8.1, and all requirements are listed in ANNEX 9.

Capacity is demonstrated by the people employed and their competence and development, equipment and process capabilities, the facilities and their design, control and management and the management system for every stage of manufacture, all backed by the necessary regulatory approvals and licences, an identifiable legal entity and records of marketing and production (included summary data confirming compliance with the product specifications) and the financial resources to sustain the organization.

As part of the bid evaluation, the following criteria for suppliers should be assessed:

- manufacturing license,
- quality certification,
- business license,
- experience in production and evidence of supply to the field of the same products being evaluated,
- financial stability (from independent audits), and
- other factors, such as after-sales service, manufacturing capacity and delivery lead times.

These may be weighted, and the weightings may vary with the value of the order and other criteria (28).

A restricted set of criteria will be used for new manufacturers, and the criteria will have to be weighted differently (see also SECTION 6.3).

7.3 Commercial evaluation of bids

The steps in the commercial evaluation of bids for RDTs are the same as for any medical device. The evaluation committee also must check that the suppliers have confirmed that they:

- are capable of providing the quantities required within the desired time frame,
- have a proven record of manufacturing products that conform to the purchaser's specifications, or similar requirements, with supporting current certifications and licences,
- are suppliers of WHO-tested products, and
- will accept the general and specific conditions of the contract, including compliance with all quality control procedures identified in the bidding documents (see SECTION 5.2).

Any supplier that has not submitted the required documentation and made other required assurances, has not adequately responded to the requests of the bidding package or is found for other reasons to be non-compliant by the evaluation committee should not be recommended for the award of the contract.

The supplier should be chosen on the basis of the following criteria:

- the product submitted (with the same product code) has been proven to have acceptable diagnostic performance in WHO product testing for malaria RDTs (as per requirement identified in the bidding document). The supplier should confirm in writing that the product submitted for the tender is the same as that evaluated in WHO product testing, even if it has the same product code,
- demonstrated capacity to supply,
- ability to meet the requirements of the contract,
- competitive product prices at corresponding Incoterm (see **SECTION 7.3.1**),
- lead time, and
- minimum order quantity.

Once the committee has identified and qualified the winning bidder, it makes a recommendation to the contracting authority to award a contract. Upon approval or endorsement of the recommendation by the contracting authority, a contract can be awarded to the winning supplier.

- ➔ *Non-specialized procurement agents and importers should not be invited to respond to the tender and should not be included in the list of potential suppliers, as they are unlikely to have experience with a 'cool chain' or other aspects of medical device importation.*
- ➔ *Suppliers should not be selected on the basis of price alone.*

7.3.1 Determinants of price and procurement costs

In evaluating bids, it is particularly important to compare the elements described below, which determine the final procurement and operational costs (21):

- goods price,
- specified Incoterms (22) of the bid for delivery to the agreed point, such as by air or sea freight in refrigerated containers, including specification of who pays for insurance, handling fees and port clearance. It is important to ensure that all bidders quote their prices in Incoterms in order to make the offers comparable for proper evaluation and adjudication,
- size, weight and volume of deliveries, which affect transport and storage requirements. The pouches and boxes in which RDTs are supplied can contribute significantly to their volume, and the choice of pack size (e.g. number of unit packs of 60 pouches per outer or transit container) can substantially affect the total volume and chargeable weight,
- cost and effectiveness of security measures in transit. Transit is covered by international freight conventions or a relevant insurance policy and not directly by the manufacturer. Even if the Incoterm leaves responsibility for transport to the supplier, freight would be subcontracted to a specialized freight forwarder,
- cost of any customization of products for use in a specific country or programme; e.g. embossment with words like: 'for public use only', 'not for sale' or the logo of the national health authority or project sponsor,
- product registration fees, as a requirement for authorization in the destination country,

- clearance and handling fees at point of delivery, which can increase in case of delayed port clearance procedures, and
 - programme support costs, or service fees, which are levied by the procurement agency if procurement is managed by one or more specialized agents.
- ➔ ***When evaluating offers from multiple suppliers, not only the goods price but all other elements should be taken into consideration to determine and compare the total cost of RDTs delivered to the central medical store or other defined point of receipt.***

7.3.2 Patents

Patent protection granted for medical devices, including in vitro diagnostic devices and malaria RDTs, under national law should be taken into account in procurement. The two possible types of patent are product patents for specific products and process patents covering the procedure by which the product is manufactured. There could be patents on individual components of RDTs (e.g. specific monoclonal antibodies), but currently no patents limit access to lateral flow testing. Contracts with manufacturers should request them to certify that there are no patents limiting the use of RDTs in the recipient country and that, in case of patent infringements, the manufacturer will be responsible for refunds if liability is incurred.

A patent gives a legal right to prevent or exclude others from manufacturing, marketing or importing an invention (which may include any element of the RDT) that has been granted patent rights by a State for a fixed period. The procedure for granting patents, the requirements placed on the patentee and the extent of the exclusive rights vary according to national laws and international agreements. To purchase necessary health products at an affordable price, countries can make use of the safeguards allowed under the agreement on trade-related aspects of intellectual property rights (TRIPS), under which compulsory licences can be granted for generic equivalents of patented products in the interests of public health (29).

Although information on patents pending or granted in countries is theoretically in the public domain, it is often difficult to locate or is outdated. For updated information on intellectual property rights, procurement entities can try to obtain information from manufacturers on patents granted and on any countries in which they have waived their patent rights or have provided immunity from suit.

- ➔ ***Patents might pose a problem in the future when new malaria RDT products come onto the market or when companies start enforcing patent rights in countries. Technical assistance (including legal assistance) should be sought when lack of information and ambiguity lead to difficulties in procuring essential health products at the lowest possible price (21).***

7.4 Awarding contracts

A contract is drawn up after successful tendering, selection and award and should give:

- technical specifications (quality and quantity),
- supply conditions and procedures (service expectations and price),
- definitions of major and minor product changes (variations),
- requirements for product registration,
- payment schedule, and
- procedures for the management of disputes.

The contract should specify the requirement for product registration. In procurements funded by the World Bank, products do not have to be registered in the recipient country before contract award (30). Registration with medical device control authorities is often lengthy and cumbersome and can delay shipment and receipt of goods; risk mitigation might include early registration as soon as the RDT is selected and choosing RDTs that meet the requirements and are already registered.

A payment schedule is usually part of the contract, to which both parties are legally bound. For example, a common international payment schedule includes an approximately 30% advance on signing the contract, 30% on delivery and 40% on final acceptance. Some procurement agents allow advance payment to suppliers only under special circumstances, which must be justified. As a rule, no negotiations are allowed on changes to product specifications or price, but many framework agreements allow volume-based discounts. Disagreements between supplier and purchaser are not uncommon, however, and usually centre on the method of payment, total funds due and time of delivery.

Payments are made to the supplier when the terms of the contract have been met, the goods have been supplied and the price charged is that specified in the contract. Contract closure is the final aspect of contract management.

In practice, signing a contract often takes longer than expected. Although standard bidding documents issued by lenders (e.g. the World Bank) can be considered leaving no possibility of misconstruction from the perspective of what is demanded and the performance criteria, suppliers and, in some cases, purchasers may be unsure about the possible ramifications of certain sections of the contract. Experts from the organization's legal department should be asked to clarify the situation. In many cases, even when the wording seems clear, suggestions from legal advisors may necessitate further negotiation between supplier and purchaser.

When a contract has been signed, those charged with managing it (i.e. the procurement department) must exert their fiduciary responsibilities to ensure that the terms of the contract are met and the purchaser's interests are protected. Claims relating to non-performance by either party to the contract should be based on information and records kept by the procurement department (31).

➤ ***Signing a contract makes the relationship between purchaser and vendor legally binding. Should any disputes arise later, the contract will serve as the basis for the agreed terms. Ambiguities in or omissions from the contract can compromise programmes or projects.***

STEP 8

Quality assurance in procurement

Quality assurance is a wide-ranging concept, constituting a total process. The purpose of quality assurance for malaria RDTs is to ensure reliable, relevant, timely results that are interpreted correctly, thereby increasing efficiency, effectiveness, enhancing clinician satisfaction, improving patient care and decreasing the costs due to misdiagnosis.

The most direct way of delivering a comprehensive quality assurance programme is to map the procurement and deployment processes from beginning to end, from RDT manufacturer to diagnosis of suspected malaria. The main components of a quality assurance plan for procurement and use are to:

- align RDT quality assurance with WHO recommendations on RDT procurement and use,
- draw up a lot-testing and field monitoring plan, which includes standard operating procedures for reporting problems such as rejection of a product,
- identify training requirement, tools and resources for health workers in RDT diagnostic testing and use of the results for patient management,
- define interventions to strengthen RDT supply and distribution, including the logistics management information system,
- develop a plan and standard operating procedures for supervision and monitoring of test performance in the field by expert microscopists at sentinel sites, and
- draw up a plan and standard operating procedures for monitoring user proficiency.

Establishing a complete quality management system will ensure that routine testing runs smoothly and will make it possible to anticipate non-routine tasks, such as procurement of non-typical items for proper RDT implementation. Costing of quality assurance should be considered a part of operational costs in a mature quality assurance programme and should be budgeted accordingly. It is important to take account of existing use of RDTs in the private sector as well as new products coming onto the market within a robust post-market surveillance system.

Quality control of individual lots of RDTs throughout their shelf-life, by appropriate standard operating procedures, has been established by WHO (see **STEP 9** and 32).

➤ ***For quality assurance of RDTs, WHO recommends nomination of a focal person at national level, who is responsible for planning and implementing the whole programme (33).***

8.1 ISO 13485 certification

RDTs are accepted for WHO product testing only from manufacturers that are certified to ISO 13485:2003 (11). This standard is required as the basis for quality assurance management of in vitro diagnostic devices for their registration and regulatory control in many places. The European CE mark for RDTs is based on certified compliance with the Directive on in vitro diagnostic devices and includes compliance with ISO 13485 certified by a notified body.

This international standard specifies requirements for a quality management system that can be used by an organization to design and develop, produce, install and service medical devices and

to design, develop and provide related services. ISO/TR 14969 (34) is a technical report intended to provide guidance for application of ISO 13485. While it is a separate standard, it is based on ISO 9001 (35).

The standard specifies requirements for a quality management system for an organization that has to demonstrate its ability to provide medical devices and related services that consistently meet customer requirements and regulatory requirements applicable to medical devices and related services.

The validity of the certificate can be checked by consulting the body that issued it. Further confirmation of the standing of the certificate can be obtained by checking the standing of the certification body with the competent government body overseeing standards for medical devices, including in vitro diagnostic devices and RDTs, in the country and specifically accrediting the certification bodies as competent to provide certification of manufacturers' competence and compliance with the standards. Competent authorities not only accredit certification bodies to certify RDT manufacturers to ISO 13485 but also directly accredit test and calibration laboratories to the ISO 17025 standard (36).

The requirements of ISO 13485:2003 certification are listed in **ANNEX 9**. The manufacturers' responsibility for the RDT does not cease once it has left their direct control. The following responsibilities, further described in **SECTIONS 8.1.1–8.1.4**, should be integrated into the procurement quality assurance systems:

- risk management (section 7.1 of ISO 13485),
- traceability (section 7.5.3.2.1 of ISO 13485),
- preservation of product, including storage conditions through to delivery (section 7.5.5 of ISO 13485), and
- feedback system (sections 7.2.3 c, 8.2.1 and 8.4 of ISO 13485).

These are reviewed below and considered further in **ANNEX 9**.

➤ ***The worldwide standard is assessing conformity with product registration and marketing approval requirements (see SECTION 6.2). The current, valid copy of the ISO 13485 certificate should be submitted as part of the tender documentation. It should be verified that the certificate has been awarded by an accredited certification body, is not out of date, applies to the site of manufacture of the RDTs and explicitly includes the manufacture of RDTs in its statement on scope.***

8.1.1 Risk management

Risk management is an integral component of the manufacturer's quality management system, as required by ISO 13485 (see section 7.1 of ISO 13485).

Risk management covers risk analysis, risk evaluation and risk control. For malaria RDTs, the components of both the manufacturer's and the procurement risk management plans should include:

- quality control procedures implemented by the manufacturers and their standard operating procedures,
- quality control requirements of procurement and funding agencies (e.g. pre-shipment lot testing),
- manufacturer's definitions of major and minor variations (see section 15.1 of ISO 13485) and procedures for notifying procurement agencies and distributors,
- criteria and procedures for product recalls, and
- production and post-production information.

The listed criteria should not be taken as exhaustive. Risk management begins with a consideration of possible risks and corresponding decisions on appropriate control measures and their implementation; the risk management plan requires demonstration and records of the entire process. The production and post-production information steps link directly to the feedback requirements of ISO 13485.

More complete lists of product and procurement vulnerabilities specific to malaria RDTs are given in **TABLES 1** and **2**. The risk management plan should include measures to prevent these vulnerabilities, rapidly identify their occurrence and recommend feasible remedial actions to minimize their consequences, if they occur.

- ***Risk management should also be a requirement of procurement quality assurance, and the two systems should complement and support each other where they overlap.***

8.1.2 Traceability and recall

Goods traceability is an essential requirement; otherwise product recall is not possible. The manufacturer is responsible for traceability up to the point of delivery.

- ***The procurement officer should ensure that traceability is clearly specified in the tender documents and that the procurement quality management system supports traceability from delivery to use.***

8.1.3 Product preservation and storage conditions

Preservation of products, including storage conditions through to delivery to the intended destination, is the responsibility of the manufacturer (see section 7.5.5 of ISO 13485).

- ***The procurement officer should ensure that preservation is clearly specified in the tender documents and that the procurement quality management system supports product preservation and control of storage conditions from the point of delivery to use.***

8.1.4 Post-delivery device monitoring

Obtaining feedback on the product is the responsibility of the manufacturer under the monitoring and measuring requirements of ISO 13485 standards and is linked to any requirement of national or regional regulations to gather post-production information on experience with the device. The management of risk similarly requires this information. The procurement officer should ensure that this is clearly specified in the tender documents and that the procurement quality management system supports the acquisition and use of product feedback throughout delivery, storage and use. For further information on the risk management requirements of ISO 13485, see **ANNEX 9**.

8.2 Prequalification

Some procurement agencies have developed prequalification schemes for malaria RDTs (37), as has WHO (33, 38). Countries may have their own prequalification schemes to assess manufacturers and to prequalify products, including diagnostics. Prequalification may be a requirement of funding and procurement agencies.

The costs can easily be prohibitive, and many countries rely on organizations that have the resources to prequalify manufacturers throughout the world and can provide a publicly available listing of such manufacturers. Prequalification requires independent product testing. (For information on laboratory accreditation for independent product testing, see **SECTION 9.2**.) WHO product tes-

ting provides results on RDTs with specified performance from manufacturers that are certified to ISO 13485, and this is a step towards prequalification.

Examination of the product dossier and inspection of the facility in which the product is manufactured are performed by qualified inspectors using recognized standards, as a complement to technical evaluation of tender documents.

FURTHER READING

- *A model quality assurance system for procurement agencies*. Geneva, World Health Organization, 2007 (WHO/PSM/PAR/2007.3).
<http://www.who.int/medicines/publications/ModelQualityAssurance.pdf>
Search: “model quality assurance procurement”
 - *RDT evaluation programme. Current programmes for RDT quality assurance*. Manila, WHO Regional Office for the Western Pacific.
http://www.wpro.who.int/sites/rdt/who_rdt_evaluation/
Search: “quality assurance malaria RDTs”
 - *Organization of national quality assurance programs for malaria RDTs*. Manila, WHO Regional Office for the Western Pacific.
http://www.wpro.who.int/sites/rdt/using_rdt/qa/
Search: “quality assurance malaria RDTs”
-

STEP 9

Quality control by lot testing

9.1 Introduction

Malaria RDTs are complex biological products made up of several components, commonly made by many manufacturers. The manufacture of each component is subject to changes, which may affect the performance of the final product. RDTs are presently made from biological materials, which are subject to batch and lot variation. The terms ‘batch’ and ‘lot’ are sometimes used interchangeably for medical devices. Sometimes, a batch number is allocated to a whole order, but large orders generally include different production lots. For consistency with accepted terminology, we refer to ‘batch’ traceability, but the term for identification of the product on the device and in the documentation should be agreed with the manufacturer.

ROLE OF RDT LOT TESTING

Lot testing of RDTs should be undertaken in order to:

- prevent poor-performing batches of RDTs from reaching users,
- identify lot–lot variation in diagnostic performance, which has been seen for most malaria RDTs,
- assess the diagnostic performance of different lots produced by the selected manufacturer, and
- provide convincing evidence to clinicians and regulatory authorities that the tests are working.

➔ ***As malaria RDTs are subject to inter-lot variation, WHO strongly recommends that a sample from each production lot be tested centrally before delivery to ensure that it meets appropriate diagnostic performance standards; this should be specified in the tendering documents specifically for pre-shipment inspection.***

Lot testing involves evaluation of the diagnostic performance of malaria RDTs from different manufacturing lots against quality control parasite panels at defined density, to ensure that they perform to the required standard. Pre-shipment testing establishes quality and performance at the manufacturing level but does not detect failures resulting from transport conditions or at the point of use. Many agencies require pre-shipment lot testing and procure only from production lots that meet the lot-testing requirement. This is currently the preferred approach, to avoid the arrival of poor-quality products in a country and consequent disposal or replacement. If pre-shipment lot testing has not been performed, testing of samples delivered to the central stores is recommended. In post-shipment lot testing, it may be difficult to replace lots that fail or perform poorly, as the responsibility might lie with the manufacturer or the forwarding agent responsible for transport to the point of use.

LOT TESTING AT DIFFERENT LEVELS OF THE SUPPLY CHAIN

- *Pre-shipment* lot testing should prove that the goods intended for shipment correspond to those specified in the tender documents. It is generally directly arranged with the manufacturer and a lot-testing centre.
- *Post-shipment* lot testing should prove that the goods shipped by the manufacturer correspond to those specified in the tender documents and that no damage has occurred during shipment or transport to the defined delivery point (often a central warehouse). It is generally undertaken after delivery of the RDTs to the central warehouse and before their distribution to the field.
- *Post-distribution* lot testing is used to investigate reports of unexpected test results in the field. It is undertaken after delivery of RDTs to peripheral health facilities.

Lot testing is more widely used in pre-shipment than in or post-shipment quality control, including monitoring of variation in RDT quality throughout the shelf-life (see **SECTIONS 9.2** and **11.2**). In lot testing, malaria RDTs are assessed for stability at the manufacturer's recommended storage temperature (until the end of their shelf-life).

Lot testing is conducted by WHO with the same parasite panels used in WHO product testing but against fewer samples. Therefore, lot testing identifies only grossly inadequate tests and cannot differentiate between tests with medium and poor performance. Lot testing is therefore not a substitute for rigorous product testing, which is a quantitative assessment of performance at different parasite densities.

➔ ***Lot testing alone is inadequate for procurement decisions, as it may lead to the approval of RDTs that have poor performance. Therefore, RDTs that have undergone full product testing should be selected. Lot testing ensures that essential performance characteristics are maintained. Ideally, it should be done in laboratories accredited by WHO.***

There is an obviously close connection between product and lot testing, and the procurement officer should view them as steps in assuring the quality of the RDT.

Positive control samples based on recombinant DNA antigens are currently under development and expected to be ready for WHO product and lot testing in the near future. Once they are validated and available for use, they might play a major role in quality control, which will probably affect the distribution and availability of lot-testing services. Accredited laboratory testing for quality assurance against a range of RDT performance measures will continue.

The growth of both product and lot testing has been significant, and their role in assuring the quality of RDTs is well established. Continued provision of the free service is not guaranteed, however, and the arrival of recombinant DNA antigen-based RDTs and further rounds of product testing will require significant funding. Procurement officers should take this into consideration in budget forecasting and take careful note of developments.

9.2 General procedure

WHO and FIND currently support two fully operational laboratories that perform lot testing:

- the Malaria RDT Quality Assurance Laboratory, Research Institute for Tropical Medicine, Muntinlupa City, Philippines, and
- the Laboratory of Molecular Epidemiology, Pasteur Institute of Cambodia, Phnom Penh, Cambodia.

RELATIONS BETWEEN PRODUCT AND LOT TESTING

Product testing involves a comparison of RDT performance against a large challenge panel, including samples of set parasite density but widely ranging antigen concentrations; it also includes samples with antigen concentrations much lower than those commonly encountered in the field and a large set of parasite-negative samples, many of which cause diseases that are differential diagnoses of malaria or known blood abnormalities. It allows relatively fine differentiation between the performance of production lots of the different products submitted for evaluation. In order for an RDT to be considered as having ‘detected’ a sample (for a panel detection score), four RDTs are tested against each low parasite density sample, none of which must fail. WHO procurement recommendations take into account the prevalence of low parasite densities in different epidemiological situations and the rigour of the panel detection score to define standards of diagnostic performance. In product testing, thermal stability is tested at a higher than recommended temperature and relative humidity (at 35 °C and 45 °C and 75% relative humidity for 45 days).

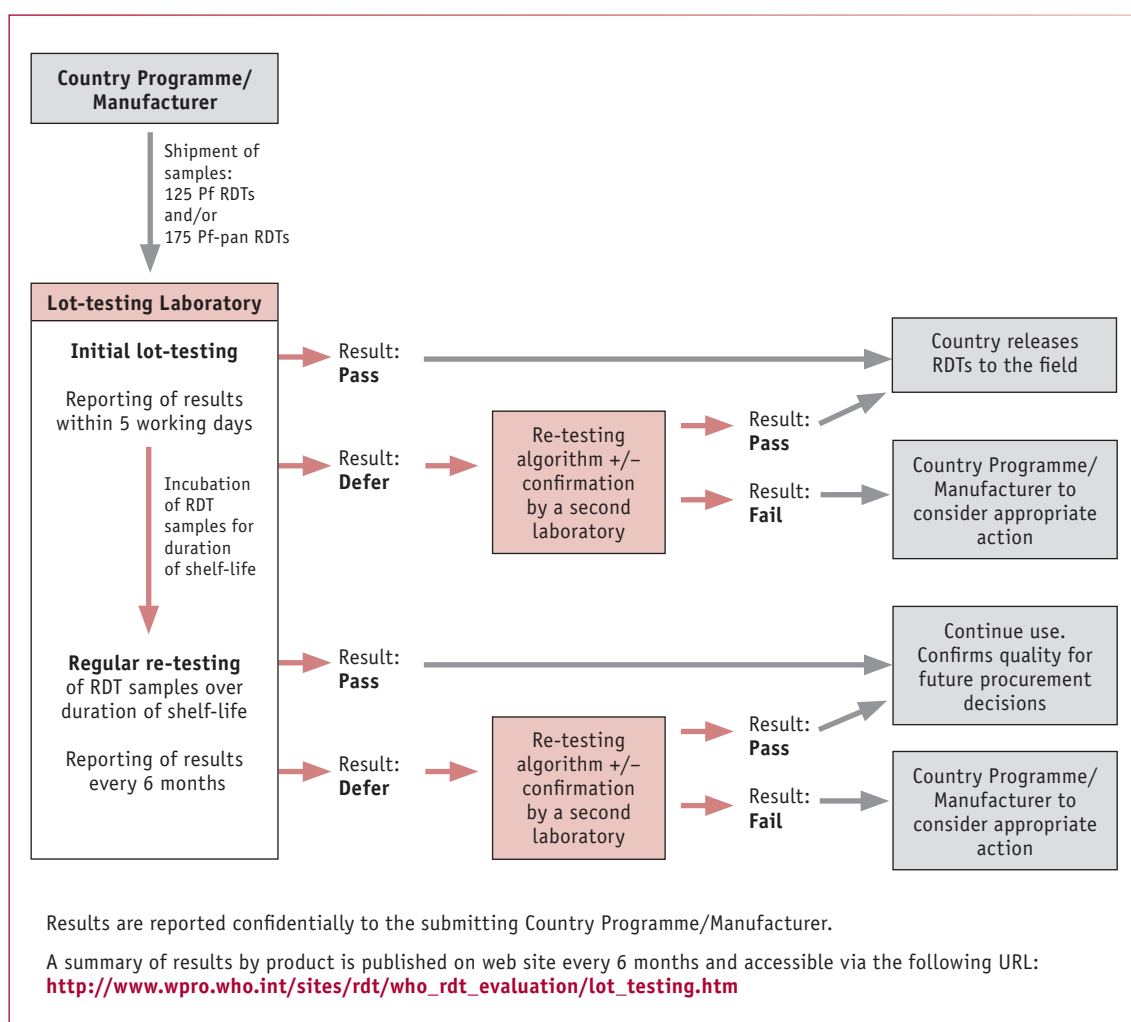
Lot testing is performed against a much smaller panel of parasite-positive and parasite-negative samples, and the antigen concentrations are closer to the middle of the concentration range used in the product testing panel. It is not designed to detect fine differences in RDT performance but to detect RDT lots that may have major defects in performance. Owing to the absence of samples with low antigen concentrations (‘hard to detect samples’) in these panels and the small number of RDTs tested, a 100% pass rate is expected. If RDTs fail on initial testing, further characterization of the extent of the problem is undertaken before a ‘fail’ notice is given. This is described in the methods manual for lot testing (39). In lot testing, thermal stability is assessed only at the storage temperature recommended by the manufacturer for the residual shelf-life of the RDT.

In addition, the WHO-FIND evaluation programme has developed local capacity for lot testing at a number of national laboratories, for example, the Centro Internacional de Entrenamiento e Investigaciones Médicas (Colombia), the Department of Medical Research (Myanmar), the Ifakara Health Research and Development Centre (United Republic of Tanzania), the Institut Pasteur de Madagascar (Madagascar), the Institut Pasteur de Bangui (Central African Republic), the Kenya Medical Research Institute (Kenya), the Universidad Peruana Cayetano Heredia (Peru), the University of Lagos (Nigeria) and the Université Cheikh Anta Diop de Dakar (Senegal). These institutions, which have undergone external quality assurance assessments through the programme, are run with national or international resources but receive technical support from WHO and FIND. They have contributed to the global malaria specimen bank held for WHO at the United States Centers for Disease Control and Prevention (13).

To apply for RDT lot testing, the requisitioner (e.g. national malaria programmes, manufacturers and procurement bodies) should complete a lot-testing request form (40) (see **ANNEX 10**) and send it to WHO/FIND at least 2 weeks before sending the RDTs. WHO/FIND nominates the laboratory that will undertake the testing and instructs the requisitioner to ship 125–175 RDTs to the selected testing centre. The RDTs are then evaluated against a small panel of parasites at high and low densities as well as against negative samples. Subsequently, the RDTs are incubated at a temperature close to the manufacturer’s specified storage temperature and are retested every 6 months until their expiry date. Initial results are available 5 days after receipt of the RDTs at the laboratory; the results of subsequent re-testing are sent regularly to the requisitioner throughout the shelf life of the RDT. For both, the lot-testing report form shown in **ANNEX 11** is used. The general procedure is shown in **FIGURE 10**.

➔ *Lot testing should be performed by reference laboratories in accordance with acceptable international guidelines. WHO lot-testing guidelines for malaria RDTs are available (39).*

FIGURE 10
Lot testing



9.3 Sampling for lot testing

The diagnostic performance of a lot is estimated by testing a randomly selected sample of RDTs from that particular lot. Sampling for independent testing should be done by either an independent accredited laboratory or by an independent sampling organization and not by representatives of the company producing the RDTs. Random sampling is required for both pre-shipment and post-shipment lot testing.

The sample, once taken, must be sealed and dispatched to the test laboratory under the sampler's supervision. At the request of the manufacturer or purchaser, a duplicate sample may be taken for use in case of disputes; this can either be sent to the test laboratory or sealed with tamper-proof tape and left at the factory. The sampling agency, either the manufacturer or an independent sampling agency, must issue a report on the sampling, detailing the protocol, identification of the cases from which samples were taken and the total number of cases offered for sampling. These terms must be included in the contract, to avoid misunderstanding and conflicts. The sampler must mark the cases from which samples were taken for buyer reference at receipt.

Guidance on sampling is widely available (41–43). Most is based on the levels of confidence that can be assigned to the risks inherent in sampling.

9.4 Reporting and interpreting the findings

The testing laboratory sends the results of the initial lot testing by e-mail within 5 working days of receipt of the RDTs to the designated contact of the requisitioner. The lot-testing report form is shown in **ANNEX 11**. The testing laboratory completes separate reports for different products and different recipients.

The report form presents the results of the initial testing as a 'pass' or 'fail'. The same form is used for reporting the results of the regular 6-monthly re-testing of the lots throughout their indicated shelf-life. For a lot of RDTs to pass a quality control assessment, all positive quality control dilutions must be positive (100%). Performance with *Plasmodium*-negative control samples should also be taken into account in interpreting the results.

The information given on the form includes summary results and guidance on interpreting the findings (44), recommendations on action and communication with the manufacturer.

FURTHER READING

- *RDT Evaluation Programme. Lot testing: Pre- and Post-purchase*. Manila, WHO Regional Office for the Western Pacific.
http://www.wpro.who.int/sites/rdt/who_rdt_evaluation/lot_testing.htm
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 - *Lot testing of malaria rapid diagnostic tests. Quality benefits all*. Manila, WHO Regional Office for the Western Pacific.
http://www.wpro.who.int/NR/rdonlyres/8DF454F7-1183-4930-8A39-80E225521AB9/0/Lot_testing_brochure.pdf
Search: "lot testing brochure RDT"
-

STEP 10

Transport, port clearance and receipt

10.1 Transport and temperature control requirements

The conditions of stowage for transport and storage must comply with the heat stability characteristics of the RDT. The buyer should decide how to apply these conditions to storage in transit, in relation to:

- what the temperature storage conditions in transit should be and whether they should be controlled, i.e. whether the RDTs should be shipped as general cargo or under ‘keep cool airway bills’,
 - clear communication of stowage in transit conditions to both: (i) the forwarding agent responsible for transport to the port in the country of receipt, including storage conditions during port and customs clearance; and (ii) the agency responsible for transport from the port of receipt to the in-country storage facilities at all levels of the system,
 - whether the temperature history should be recorded, just as maximum and minimum values or with a complete timeline that shows durations at different temperatures, and
 - what action should be taken if the temperature record indicates that maximum storage temperatures have been exceeded; the record can assist decision-making by providing information on the duration of temperature excursions above the maximum permitted values.
- *Procurement officers should guard against the risk that the shippers will consider the lower temperature limit a requirement for controlled temperature storage, with all the potentially unnecessary costs this might occur. Contracts and shipping instructions and all documentation and labelling should be explicit on this issue.*

10.2 Port and customs clearance

Port and customs clearance represent many potential pitfalls that can seriously affect malaria RDTs, particularly in relation to potential exposure of tests to high storage temperatures that could affect their diagnostic performance. Customs clearance is the set of functions undertaken by a national customs authority that includes:

- processing import, export and transit declarations,
- assessing the origin, value and classification of goods,
- collecting and processing duties and fees,
- physically inspecting, examining and releasing cargo,
- conducting post-clearance audits,
- processing urgent consignments, and
- administering waivers and exemption schemes and drawback (re-exportation) schemes (45).

Goods may fall under the same import category yet be variously subject to (value-added) tax (46). The cost of handling these processes effectively is part of the cost of procurement.

Specific consideration should be given to:

- consulting with the main procurement department for regulations, to enable informed logistics planning, including shipment and clearance,
- allocating customs and clearance tasks to senior or experienced personnel,
- meeting with representatives of the national regulatory agency, procurement and customs departments to discuss requirements at an early stage of the procurement process, and
- ensuring that appropriate (15–20 °C) storage conditions are provided.

Above all, it is important to ensure that prompt notice of receipt is given to the consignee by the receiving authorities, in order to avoid any loss of critical time.

- *A good deal of effort is required weeks in advance of a shipment to ensure that all the paperwork is complete, as this can be vital to a smooth passage through the port of arrival and through customs. As malaria RDTs are vulnerable commodities, attention should be paid to ensuring that they are retained at the port of entry in storerooms that are not exposed to high temperatures.*
- *The procurement officer should be conversant with the country's import requirements. Port and customs clearance procedures change over time and can be complex.*

10.3 Receipt of each shipment

A number of problems can present at this stage, but most can be circumvented or solved on the basis of clear recommendations and good preparation (46).

- Documentation: Keep track of documentation requirements as part of an effective overall procurement quality assurance approach, and ensure compliance with changes of regulations over time.
- Corruption: The best preventive measure is to have the tax valuation approved before the goods leave the port of origin. This is possible when the destination country has pre-shipment inspection in place. Procurement experts have noted that when pre-shipment inspection exists and is done scrupulously, goods move quickly through customs (46).
- Capacity of the consignee: The capacity of the recipient to receive imported goods is critical to smooth clearance. The best preventive measures include using partners with established capacity.
- Capacity of clearance agent or freight forwarder: Preventive action is based on good selection of an agent or forwarder on the basis of their presence in more than one country, the volume of shipments processed, the size of the staff and recommendations from other customers.
- Capacity of the port of receipt: Delays in port often occur because of handling and transport issues that are outside the customs clearance process, often associated with lack of port organization and equipment and poor inland transport. A wide range of preventive actions can be taken based on understanding the port process, issues and causes to find appropriate solutions that stop short of finding another port (46).

10.4 Verification on receipt of shipment

After the shipment has passed into the hands of the purchaser, the planned verification inspections should be undertaken, covering visual inspection, product sampling and verification for damaged, incomplete or expired RDTs.

Visual inspection:

- Count the number of RDT boxes received and compare the number with the delivery note.
- Check for obvious damage to the outer carton, such as tears or cuts on the box or crushed boxes.
- Check the expiry date.

Product sampling:

- Select one or two cartons from each lot received, and open them to verify the contents.
- Select two to three kit boxes that are not next to each other, in each selected carton.
- Open the kit boxes to check that the individual packaging has not been damaged. For RDTs that come in kits with one buffer bottle for several tests, ensure that the buffer has not leaked; if it has leaked into one or more boxes, open more boxes from the same lot to determine whether the whole lot is affected.
- Open one RDT envelope (individual packaging) from each of the selected kit boxes to ensure that all the components specified by the manufacturer (e.g. cassette or dipstick, blood transfer device, lancet, buffer) are in it. If any component is missing, open more envelopes from different kits (but the same lot) to determine whether the problem affects the whole lot. Discard all opened test envelopes and their contents.
- If the inspected RDT boxes are in satisfactory condition, reseal them and write on the box the number of individual tests remaining, noting that they have been checked for inspection.

Samples taken at this time include those needed for post-shipment lot testing (see **STEPS 9** and **11**).

Damaged, incomplete or expired RDTs:

Some of the RDT kits received may have already expired, been damaged during shipping or lack necessary components (incomplete kits).

- Immediately separate the damaged, incomplete or expired products from the usable products; put the unusable products in a clearly marked space separate from the usable products.
- Immediately report any defects to the institution that ordered the RDTs (e.g. ministry of health, nongovernmental organization); they will notify the manufacturer about the problem.
- Never issue damaged, incomplete or expired products to health facilities. If you are unsure whether a product is damaged, check with someone who knows.

It is essential to obtain an independent survey report from local independent auditors. Without this, the chances of obtaining a settlement or replacements are greatly reduced, and there will be little chance of obtaining replacements from the manufacturer without lengthy legal negotiations.

10.5 Batch traceability and recalls

A batch might have to be recalled for various reasons. Product recall may originate from the procurement management unit after reports of failed RDTs from the lot-testing programme or after reports of quality problems from the manufacturers. Actual product recall is not the responsibility of the procurement management unit and can be initiated only by the regulatory authorities in conjunction with the manufacturer. The manufacturer has the primary responsibility under ISO 13485:2003 (11) for ensuring that all distribution records maintain batch and lot traceability up to country level, to facilitate product recall (see **SECTION 8.1.2**).

- ➔ ***Recalls depend on reliable stock records containing batch data and allow batch traceability throughout the supply chain. The responsibility for maintaining batch traceability and recall in the rest of the supply chain rests with the supply management team and is a vital element of the logistics management and information system and the quality assurance systems.***

STEP 11

Monitoring

11.1 Supplier performance

As part of their quality assurance system (3), procurement agencies should monitor supplier performance and maintain their own lists of qualified suppliers. As qualification of RDT manufacturers includes ISO 13485 certification, manufacturers should be asked to provide an authorized copy of their ISO certificate for first addition to the list of qualified suppliers; the renewal date should be added to the supplier records, and the certificate should be verified from a new certified copy sent by the supplier when it is due for updating.

Indicators for monitoring and evaluating procurement of antimalarial supplies at different levels have been suggested (47). Examples of RDT-specific outcomes that could be monitored include:

- appropriate and effective ‘cool chain’ shipment and storage (where required),
- shelf-life management and available remaining shelf-life on receipt,
- product change management and transparency of changes in coding, and
- change of manufacturing site.

Changes to kit components can have significant effects on use that are quite unrelated to RDT performance per se. When these have not been acknowledged in the product description or codes, problems can occur in use of the RDT. Some funding agencies consider a product from a different manufacturing site as a new product; prequalification is valid only for a product manufactured at a specific site, and products manufactured at different sites would be subject to separate prequalification.

As in the procurement of other commodities, it is incumbent on the procurement department to monitor contract performance and identify any irregularities or non-performance indicators. For the supplier in particular, the following parameters should be monitored:

- procurement lead time,
- delayed orders,
- correctness and completeness of product-related documentation,
- number of batches that failed quality control testing,
- number of variations from agreed specifications,
- responsiveness to queries, and
- percentage increase in time to finalize the contract amount due to changes.

➤ **Supplier performance monitoring should be integrated with agreed definitions of major and minor variation (see SECTION 11.2).**

11.2 Product variations

11.2.1 Major and minor variations

Variations are classified as major or minor in relation to the effect they have on the diagnostic performance of a product. It is essential to include clear definitions and appropriate handling procedures in the supply contract (SECTION 7.4), and all changes should be notified to the buyer in advance. The effects of major and minor variations should be described in the risk management plan elaborated by the supplier (see SECTIONS 6.3 and 8.1.1). The manufacturer is responsible for putting in place and managing control measures based on the significance of the risk (see SECTION 8.1.1).

- *Minor variations*, which do not affect the diagnostic performance of the kit, might include changes in packaging, small changes in ancillary items (e.g. the size of the dispenser for the buffer solution).
- *Major variations* include for example a change in the source of monoclonal antibodies or of the nitrocellulose strip or a change in the composition of the buffer solution and the number of drops required.

The definitions that the manufacturer uses in risk management should be the starting point for categorizing ‘major’ and ‘minor’ variations. Any discrepancy between user experience and the manufacturer’s definitions should be resolved before the contract is signed and should be used by the manufacturer to improve the risk management plan. Agreement on definitions of variation allows a clear statement of acceptable and unacceptable variation and careful assignment of responsibilities for detecting and handling variation (see SECTION 11.2.2).

11.2.2 Detecting and handling variations

The quality assurance system should state explicitly in readily available documents what acceptable minor and unacceptable major variations are and how to detect them at all stages of the procurement cycle, with clear examples. The document should also provide instructions on what to do if variation is found and to whom it should be reported. As part of the contract with the supplier, appropriate requirements should be specified for communication of planned changes (product variations), including prior approval for agreed categories of change.

Deciding on whether variation has occurred can be straightforward when a clear macroscopic change presents, such as different packaging or cartridge or its labelling. These are examples of noncompliance with contractual requirements. Detecting variations in RDT products in a sample of tests taken from a specific production lot sampled at a warehouse can be problematic, and expert help may be needed. On the basis of that assessment, a decision is made whether to continue use or to appropriately segregate the product under the authority of a senior member of the procurement management unit with explicit responsibility in their terms of reference. Handling the variation must include steps to ensure the continuity of supply while the causes are being investigated and corrective action..

The final step is to record and evaluate the root cause and, where possible, to take corrective action to prevent its recurrence. If it represents a simple mistake in supply, the consequences may be serious in the short term but can be corrected without significant change in the manufacturing process.

FURTHER READING

- *Quality management system – medical devices – guidance on the control of products and services obtained from suppliers*. Global Harmonization Task Force, 2008. GHTF/SG3/N17:2008
<http://www.ghtf.org/documents/sg3/sg3final-N17.pdf>
Search: “**medical device guidance suppliers GHTF**”
 - *Implementation of risk management principles and activities within a Quality Management System*. Global Harmonization Task Force, 2005. GHTF/SG3/N15R8
<http://www.ghtf.org/documents/sg3/sg3n15r82005.pdf>
Search: “**implementation risk management GHTF**”
 - *ISO 14971:2007 Medical devices – application of risk management to medical devices*. Geneva, International Organization for Standardization.
-

STEP 12

Continuous improvement

Good practice in both selection and procurement of RDTs, as expressed in the quality management system for procurement (3, 11), should aim at continuous improvement by:

- proper handling of all deficiencies in the RDT detected during the procurement process,
- effective action to remove the cause of the deficiencies, and
- anticipatory action based on the lessons learnt.

The effectiveness of these three steps will depend on:

- how well the selection and procurement processes for RDTs are monitored by appropriate lot testing, collection of feedback from national malaria control programmes and users, complaint handling by manufacturers and distributors and a system for auditing the entire process;
- collection and use of information on deficiencies, including real or suspected issues of poor diagnostic performance and other findings from an auditing system;
- review of the effectiveness of actions to handle the deficiencies, correct the cause and prevent recurrence;
- review of the quality and completeness of the information collected to monitor the RDT selection, procurement and distribution systems up to the central storage facilities; and
- review of the risk management actions in relation to product quality and procurement that could be taken to prevent potential failures of diagnostic performance at the point of use.

Well-established tools for team-based problem-solving and process improvements are readily available and should be used as part of the RDT quality management system. They are packaged under a number of management names (e.g. '6 sigma'). Training in use of these systems is not usually provided, however, and effort is required to acquire them, adapt them and use them effectively to monitor the RDT selection, procurement and central distribution systems.

When these tools are linked to the priorities and objectives of programmes for RDT use, such as cost minimization, high RDT diagnostic performance and improvement of the procurement process, they can improve the effectiveness of RDT procurement and supply systems. The programmes deploying RDTs will benefit and so will the patients in need of diagnosis and treatment of malaria.

FURTHER READING

- *Basic concepts: continuous improvement – articles*. ASQ, Milwaukee, USA
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Search: “continuous improvement articles”
 - *Continual improvement*. Chartered Quality Institute, London, UK
<http://www.thecqi.org/Knowledge-Hub/Resources/Factsheets/Continual-improvement/>
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<http://www.who.int/medicines/publications/modelqualityassurance.pdf>
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http://whqlibdoc.who.int/publications/2010/9789241564106_eng.pdf
9. *WHO guidelines for the treatment of malaria*. Geneva, World Health Organization, 2010.
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Annexes



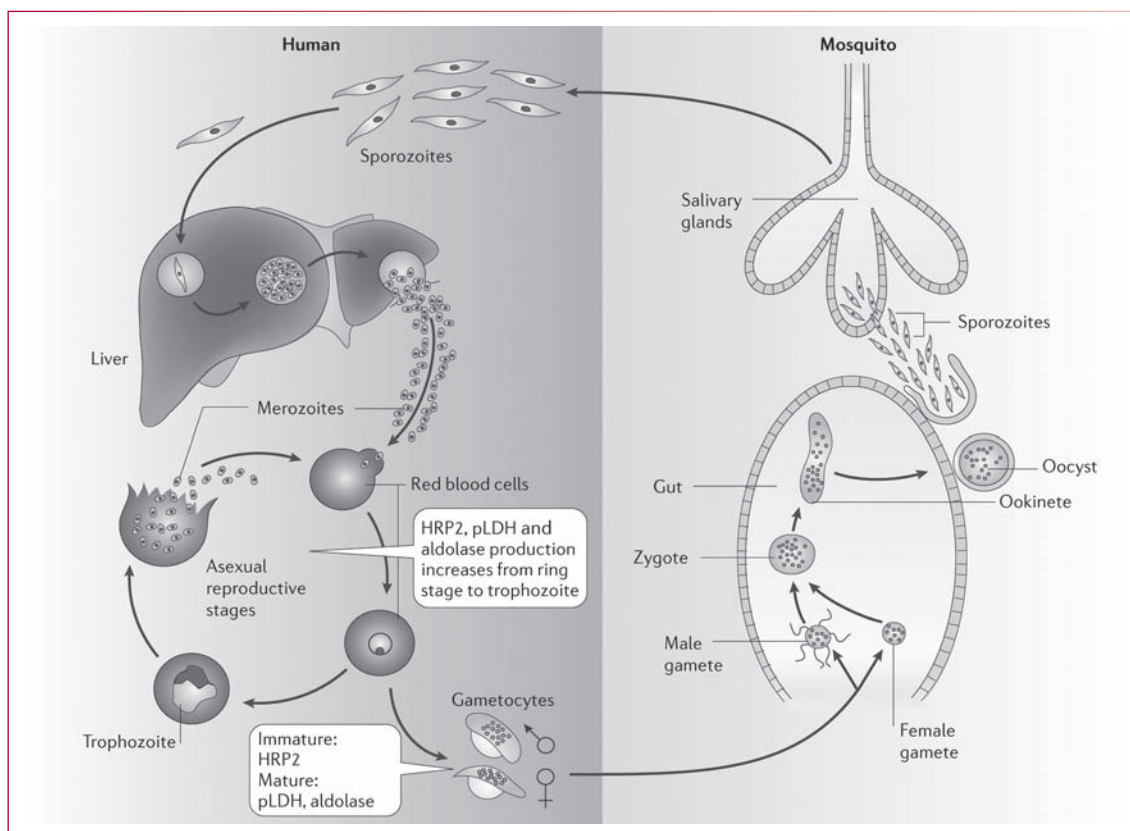
ANNEX 1

Antigen production during the *Plasmodium* life cycle

A rapid diagnostic test for malaria is a lateral-flow immunochromatographic device for detecting specific proteins, i.e. HRP2, pLDH and aldolase, that are produced during the parasite's development cycle in the human host. The malaria parasite's life cycle (**FIGURE A1**) depends on two hosts: the female anopheline mosquito and the human being. Mosquitoes become infected with the parasite when they feed on a person whose blood contains gametocytes, the sexual forms of the parasite. Gametocytes develop in a number of steps in the mosquito, until, on rupture of the oocyst form, sporozoites are released and migrate to the mosquito's salivary glands, from where they are injected into the human body by the bite of the mosquito. Sporozoites enter the human host's bloodstream and are carried to the liver, where they multiply and develop into schizonts, which, upon rupture, release merozoites into the bloodstream. Merozoites invade red blood cells and, nourished by the haemoglobin, develop from ring stages to trophozoites.

FIGURE 11

RDT target antigens produced during the *Plasmodium* life cycle



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During this process, increasing amounts of HRP2, pLDH and aldolase antigens are produced and released into the bloodstream. Upon rupture of the infected red blood cells, further merozoites are liberated, which infect additional red blood cells. The cycle of red blood cell invasion continues, resulting in increasing levels of parasitaemia and antigen production. Some merozoites differentiate into micro- and macrogametocytes, the male and female forms of gametocytes, respectively, which produce HRP2 in their immature stage, while pLDH and aldolase are generated in the mature stage. With the ingestion of the gametocytes by another female anopheline mosquito, the cycle of malaria transmission continues.

HRP2 antigen may persist for a few weeks after elimination of viable malaria parasites from the blood, while pLDH and aldolase are generally cleared within 5–6 days.

ANNEX 2

Mechanism of action of rapid diagnostic tests for malaria

RDTs rely on the capture of dye-labelled antibodies to produce a visible band on a strip of nitrocellulose. They are described as ‘lateral-flow immunochromatographic antigen-detection in vitro diagnostic devices’, a classification recognized by medicines regulatory authorities worldwide as a class of medical devices. In malaria RDTs, if the blood contains the target malaria antigen, the dye-labelled antibody first binds to the parasite antigen, and the resultant antigen–antibody complex is captured on the strip by a band of bound antibody, forming a visible line (test line) (FIGURE A2a).

The antibodies bound to the nitrocellulose strip are typically monoclonal immunoglobulin M or G of animal origin. Antibodies specific to the target antigen of the RDT are bound to the nitrocellulose strip, to constitute the test band. Antibodies targeting the dye-conjugate antibodies (labelled antibodies) are bound to the nitrocellulose to constitute the control band. The ‘capture antibodies’ are the antibodies that are bound to the nitrocellulose strip and bind to the complex parasite antigen–antibody complex and to dye-labelled antibody. The ‘signal antibodies’ are the free dye-labelled antibodies that bind to the parasite antigen targeted by the RDT.

Dye-labelled antibody specific for the target antigen is present on the lower end of the nitrocellulose strip or in a well provided with the strip. Antibody, also specific for the target antigen, is bound to the strip in a thin (test) line, and antibody specific for the labelled antibody is bound at the control line.

Phase 1. Haemolysis and antigen recognition by conjugate antibody

After the blood has been transferred into the sample well, the first step of the test consists of mixing the patient’s blood with a lysing agent (buffer solution) in the same or a different (buffer) well. The resulting rupture of red blood cells releases more parasite protein. The dye-labelled antibody, either in the well or on the strip, may then bind to the target antigen.

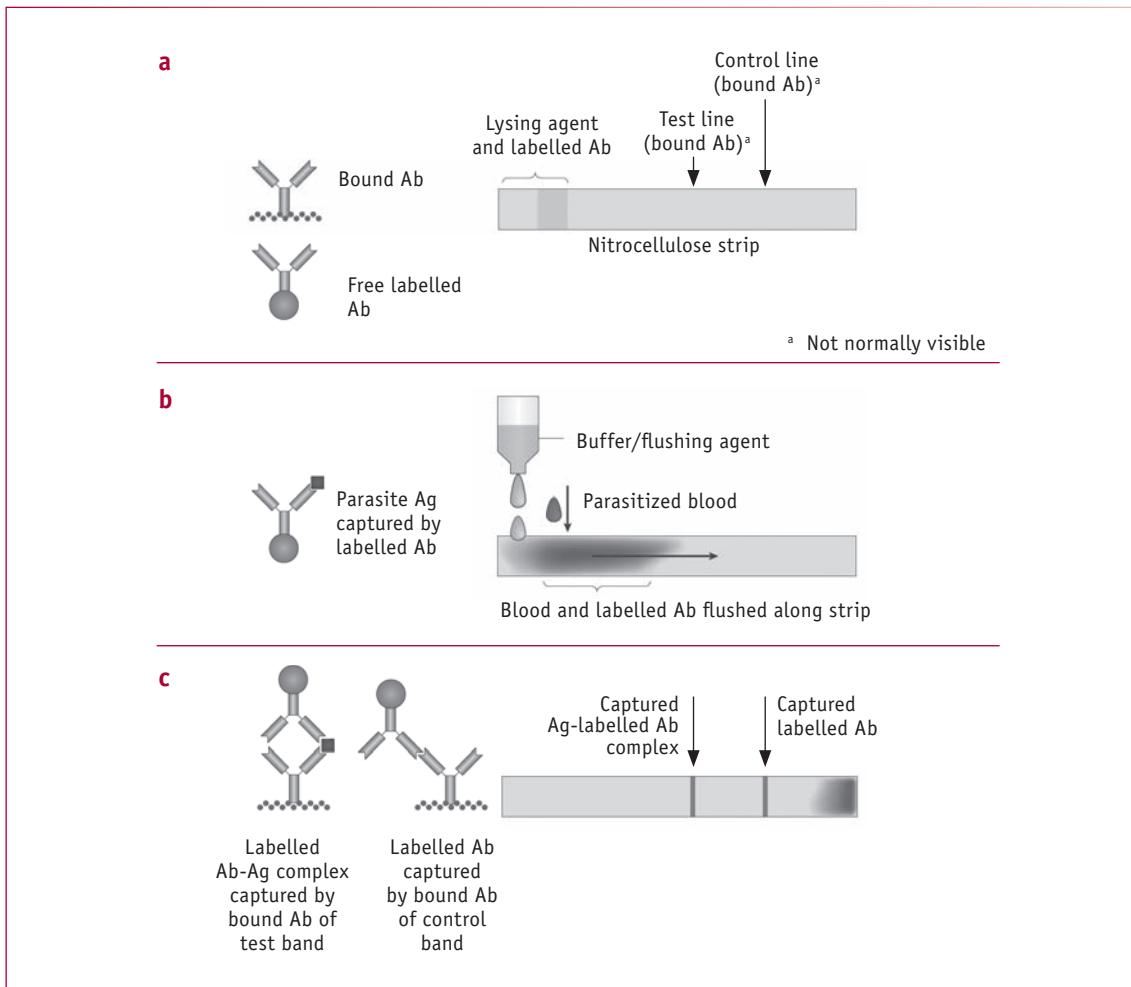
Phase 2. Migration of antigen–antibody conjugate along the nitrocellulose strip

Blood and buffer placed on the strip or in the well mix with the labelled antibody and are drawn up the strip across the lines of bound antibody (FIGURE A2b).

Phase 3. Binding to test and control lines

If antigen is present, the labelled antibody–antigen complex is trapped on the test line. Other labelled antibody is trapped on the control line (FIGURE A2c). If sufficient labelled antibody accumulates, the dye labels become visible to the naked eye as a narrow line.

FIGURE 12
Components and mechanism of RDT for malaria



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ANNEX 3

Example of minimum timelines required for the RDT procurement process

The right hand diagram shows an example of minimum timelines required for the procurement process of quality rapid diagnostic tests for malaria. The listed duration of each procurement step may vary from country to country and should only be considered as indicative.

Procurement step	Approximate duration	Month 1				Month 2				Month 3				Month 4				Month 5				Month 6				Month 7			
		Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 9	Week 10	Week 11	Week 12	Week 13	Week 14	Week 15	Week 16	Week 17	Week 18	Week 19	Week 20	Week 21	Week 22	Week 23	Week 24	Week 25	Week 26	Week 27	Week 28
Step 1: Key requirements for RDT selection	1 week																												
Step 2: Estimating needs	1 week																												
Step 3: Budgeting and budget components	1 week																												
Step 4: Defining technical specifications	1–2 weeks																												
Step 5: Procurement method and tender documents	1–2 weeks																												
Step 6: Inviting tenders	12 weeks																												
Step 7: Evaluating bids and awarding contracts	4 weeks																												
Step 8: Quality assurance in procurement and use	continuous																												
Step 9: Quality control by lot testing ^a	3–4 weeks																												
Step 10: Transport, port clearance, and receipt	4 weeks																												
Step 11: Monitoring (supplier and product)	9 weeks																												
Step 12: Continuous improvement	continuous																												

^a Consider sufficient time for contacting the lot testing programme (2 weeks before planned shipment of samples) and shipment of samples; lot testing results are available within 5 working days upon receipt of samples at the testing laboratory

ANNEX 4

Panel detection score and diagnostic sensitivity

The diagnostic performance of malaria RDTs, as measured from the panel detection score ('detection rate' in the WHO/FIND round 1 evaluation) against the challenge panel (samples of wild-type *P. falciparum* and *P. vivax* diluted at 200 and 2000 parasites per microlitre), may not be directly related to the sensitivity of the test in clinical testing. Several components of malaria RDTs are vulnerable to variation in manufacturing quality, and such variations may affect both the panel detection score and the sensitivity (see 'Determinants test performance' in the **INTRODUCTION** to this document). Variations in the manufacture of these components may result in lot-to-lot differences, which affect diagnostic performance, i.e. both panel detection score and sensitivity. It is important to test lots before their distribution to the field, to ensure that the expected performance is maintained (**STEP 11**).

Other factors may affect performance testing in the laboratory differently from field trials and may explain any discrepancy between panel detection scores and sensitivity in published field trials:

Table 6. Reasons for discrepancy between panel detection score and sensitivity	
Factor	Effect
Exposure to extreme temperatures	High temperatures accelerate degradation (deconjugation of the signal antibody–dye complex, detachment of capture antibody from the wick, and change the binding sites of antibodies and the nitrocellulose).
	Freeze-thawing may have similar effects.
Age and storage of blood sample	Stored blood may lose antigen activity; early lysis and protein coagulation can inhibit flow.
	The rate of loss of antigen activity varies among antigens.
	Lysis of cells can occur during mixing and storage.
Preparation of dilutions	Cell lysis and aggregation of parasitized cells can affect flow.
Visual acuity of technician	Can affect reading of faint test lines at low parasite density.
Patient and parasite	Parasite density affects sensitivity.
	Parasite density and parasite load (including sequestered parasites) determine antigen levels.
	Antigen production varies during the parasite life cycle and between parasite strains.
	Previous treatment and its effectiveness varies among patients.
	Factors that cause false-positive results can vary among patients.
	Antigen activity may be different in wild and cultured parasites.
Reference standard (microscopy or PCR)	Poor sensitivity reduces apparent RDT specificity.
	Poor specificity reduces apparent RDT sensitivity.

The parasite density, and in particular the population tested, affects the clinical sensitivity of the RDT. If most parasite-positive patients have high parasitaemia, even RDTs that had only a moderate panel detection score at 200 parasites per microlitre may have high sensitivity in clinical testing. Even in areas with high transmission and strong malaria immunity, however, the population may include people with low parasite densities but clinically significant infections (e.g. young children, pregnant women, people regularly using bed nets, immigrants and people with reduced immunity). The ability to detect infections with low parasite density reliably is important in all settings.

Small differences in panel detection scores among the better-performing RDTs in an evaluation are unlikely to result in noticeable differences in clinical sensitivity; other issues, such as stability, cost or ease of use and manufacturing capacity may be more important factors in selecting a test.

ANNEX 5

Elements of supply management and quantification

Supply pipeline

The physical size of stores at each level is determined by the demand for items that they have to distribute and by the supply frequency. The stock levels within the supply system and the number of supply points at each level constitute the supply pipeline. The number of levels, the frequency of requisition and delivery and the amount of safety stock at each level influence the number of RDTs needed to fill the supply pipeline.

Calculating safety stocks

As it is impossible to estimate the requirements completely accurately and to be certain of the supplier's performance, a certain stock of RDTs (inventory) is needed to absorb fluctuations in supply and demand and to reduce the risks of stock-outs. As high stock levels increase inventory costs (personnel, storage, as well as risk for spoilage, expiry and theft), most public supply systems must calculate the minimum 'safety stock' to protect against stock-outs.

The safety stock is calculated by multiplying the adjusted average monthly consumption by the expected lead time, from the formula:

$$SS = Ca \times LT$$

- **SS** is the safety stock
- **Ca** is the average consumption, adjusted for stock-outs
- **LT** is the lead time (from order to delivery in the warehouse), with the same unit of measure, often months

In the example shown in **TABLE A3**, the consumption in the period 15 September 2005 to 14 November 2005 was $120 + 400 - 305 = 215$ unit forms (boxes containing 30 RDTs each).

Stock record forms are used to calculate the actual consumption rate, taking into account the opening stock (the stock in inventory at the beginning of the period for which the consumption is calculated) plus all new amounts received during the period, minus the closing stock (the stock in inventory at the end of the period for which the consumption is calculated). If, during the same period, there have been days of stock-out for the item in consideration, the consumption should be adjusted accordingly. If this is not done, the reported consumption will be an underestimate of the true requirements for the product. Consumption data are required in order to calculate both the safety stocks and the quantity of products to be re-ordered.

Table 7. Stock record card

Product name:				Target species:		
Product code / Catalogue no.:				Antigen:		
Packaging:				Unit price:		
Date	Source or recipient	Quantity received	Quantity issued	Balance	Expiry	Signature
15/09/05	Inventory			120	06/2006	
17/09/05	Clinic A		10			
23/09/05	Health centre A		30			
25/09/05	Clinic B		10			
26/09/05	Clinic C		10			
01/10/05	Hospital		40			
03/10/05	Health post A		5			
03/10/05	Central medical store	400			07/2007	
05/10/05	Clinic B		10		06/2006	
08/10/05	Health centre A		30		5-06/2006 25-07/2007	
12/10/05	Clinic A		10			
15/10/05	Clinic C		10			
23/10/05	Hospital		40			
29/10/05	Health post B		5			
01/11/05	Health post A		5			
14/11/05	Inventory			305		

Time and quantity for re-ordering

When: once the stock has reached a minimal (re-order) level

Amount: Once the basic inventory has been established, the number of RDTs to be ordered is calculated on the basis of a 'pull system', the adjusted average monthly consumption multiplied by the sum of the lead time and procurement period plus the safety stock levels after removal of the latter from the stock on order and the stock in inventory. This is expressed as:

$$Q_o = C_a \times (LT + PP) + SS - (S_i + S_o)$$

- **Q_o** is the quantity of RDTs to be re-ordered in the next procurement period
- **C_a** is the average monthly consumption, adjusted for stock-outs
- **LT** is the lead time (expressed in months)
- **PP** is the procurement period (expressed in months)
- **SS** is the safety stock
- **S_i** is the stock in inventory (on hand)
- **S_o** is the stock on order but not yet received

The above formula can be used to manage stock levels in warehouses at central level (e.g. a central medical store), intermediate level (e.g. provincial, district warehouse) or peripheral level (i.e. deposits in health facilities serving multiple community health posts). For all these levels, the 'consumption' for a specific period should be calculated from:

$$\text{consumption} = \text{opening stock} + \text{supplies received} - \text{closing stock}$$

If major seasonal variations are expected to influence the consumption of malaria RDTs, as in areas with highly seasonal malaria transmission, the consumption should be corrected for the expected variation. This can be expressed as a multiplication factor; for example, 1 = no variation expected; 0.5 = 50% expected reduction; and 1.5 = 50% expected increase (*I*).

The 'procurement period' is used mainly at central level, to include all the procurement time that precedes the placement of orders with the manufacturer (e.g. preparation of the tender, floating of the tender, evaluation of bids, contract with manufacturers). This should be considered only for central-level warehouses.

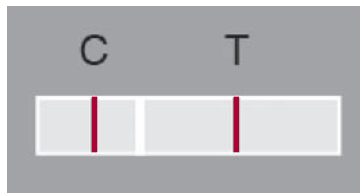
Reference to Annex 5

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http://whqlibdoc.who.int/publications/2009/9789241598088_eng.pdf

ANNEX 6

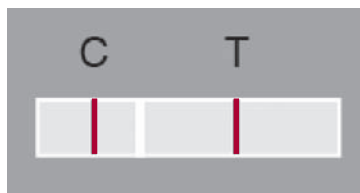
Control and test line sequence

Common types and sequences of control lines (C) and test lines (T) on RDT cartridges.



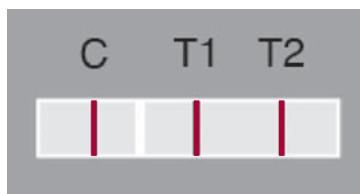
Type A: Malaria generic Pf RDT

Results window: C, control line; T, test line with bound HRP-2 antibody



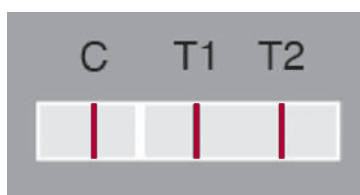
Type B: Malaria generic major *Plasmodium* species (pan) RDT

Results window: C, control line; T, test line with bound pan-specific antibody



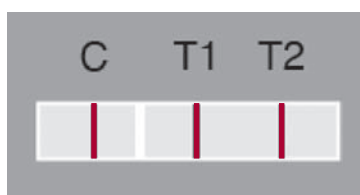
Type C: Malaria generic pan-Pf RDT

Results window: C, control line; T1, test line with bound pLDH-pan or aldolase antibody; T2, test line with bound HRP2 or Pf-specific pLDH antibody



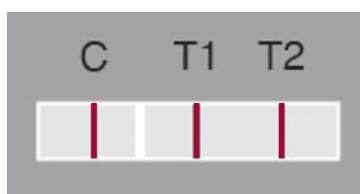
Type D: Malaria generic Pf-pan RDT

Results window: C, control line; T1, test line with bound HRP2 or Pf-specific LDH antibody; T2, test line with bound pLDH-pan or aldolase antibody



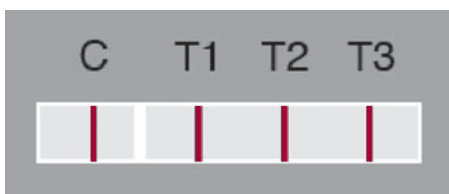
Type E: Malaria generic Pv-Pf RDT

Results window: C, control line; T1, test line with bound *P. vivax*-specific pLDH; T2, test line with bound HRP-2 antibody or Pf-specific LDH antibody



Type F: Malaria generic Pf-Pv RDT

Results window: C, control line; T1, test line with bound HRP2 or Pf-specific pLDH antibody; T2, test line with bound *P. vivax*-specific pLDH



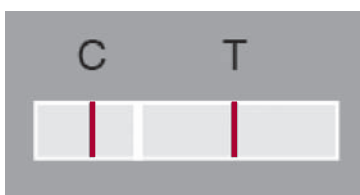
Type G: Malaria generic pan-pv-pf RDT

Results window: C, control line; T1, test line with bound pLDH or aldolase antibody; T2, test line with bound *P. vivax*-specific pLDH; T3, test line with bound HRP2 or Pf-specific pLDH antibody



Type H: Malaria generic VoM1-pf RDT

Results window: C, control line; T1, test line bound with pLDH specific for non-*P. falciparum* (*P. vivax*, *P. ovale* and *P. malariae*); T2, test line with bound HRP2 or Pf-specific pLDH antibody



Type I: Malaria generic pv RDT

Results window: C, control line; T, test line bound with *P. vivax*-specific pLDH

References to Annex 6

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ANNEX 7

Examples of regulatory device labelling and information requirements

The Directive of the European Commission on in vitro diagnostic medical devices (1) and the Global Harmonization Task Force (2) provide a complete set of requirements for labelling and for the product information of diagnostic devices. The label must bear the following particulars, which may take the form of symbols as appropriate.

Table 8. Labelling

Combined, rationalized labelling requirements	European Commission in vitro diagnostic medical devices Directive (1)	Global Harmonization Task Force requirements (2), 5.2 Content of labelling
Manufacturer details (e.g. name, address, authorized representative and contact details)	Name or trade name and address of manufacturer; the labelling must also include the contact details of the 'local' (country or region) 'authorized representative'	Name or trade name and address of manufacturer and, if appropriate, a telephone or fax number or web site address to obtain technical assistance
Product name and unique product identification (e.g. code or catalogue number)	Details strictly necessary for the user to identify the device and the contents of the packaging uniquely	Sufficient detail for the user to identify the device and, when this is not obvious, its intended purpose, user and patient population; also, where relevant, the contents of any packaging
Batch or lot number, serial number	Batch code, preceded by the word 'lot'	Indication of batch code and lot number to allow appropriate actions to trace and recall the devices Indication of date of manufacture; may be included in the batch or lot number or serial number
Expiry date, shelf-life; intended use or purpose	If necessary, an indication of the date by which the device or part of it should be used, safely, without degradation of performance, expressed as year, month and, when relevant, day, in that order	Unambiguous indication of date until which the device may be used safely, expressed at least as year and month (e.g. on devices supplied as sterile, single-use, disposable devices or reagents), when relevant
Clear indication of in vitro diagnostic medical device status of the product	When appropriate, a statement indicating the in vitro use of the device	Performance intended by the manufacturer
Storage and handling instructions	Any particular storage or handling conditions When applicable, any particular operating instructions	When relevant, storage conditions and shelf-life after first opening of the primary container, with storage conditions and stability of working solutions Indication on external packaging of any special storage or handling conditions Details of any further treatment or handling needed before the device can be used (e.g. sterilization, final assembly, calibration, preparation of reagents or control materials)
Warnings, precautions	Appropriate warnings or precautions to take	Any warnings, precautions, limitations or contraindications

Table 8. Continued		
Combined, rationalized labelling requirements	European Commission in vitro diagnostic medical devices Directive (1)	Global Harmonization Task Force requirements (2), 5.2 Content of labelling
Clear statement of 'for performance evaluation only' or 'presentation' or 'demonstration', when applicable	In case of devices for performance evaluation, the words 'for performance evaluation only'	If the device is intended for premarket clinical investigation or, for in vitro diagnostic medical devices, performance evaluation, only, an indication of that situation If the device is intended for presentation or demonstration purposes only, an indication of that situation
Documentation		Date of issue or latest revision of instructions for use and, when appropriate, an identification number

Table 9. Product information		
Combined, rationalized labelling requirements	European Commission in vitro diagnostic medical devices Directive (1)	Global Harmonization Task Force requirements (2), Content of information
Safe use information	"As far as practicable and appropriate, the information needed to use the device safely and properly must be set out on the device itself and/or, where appropriate, on the sales packaging. If individual full labelling of each unit is not practicable, the information must be set out on the packaging and/or in the instructions for use supplied with one or more devices. "Instructions for use must accompany or be included in the packaging of one or more devices. "In duly justified and exceptional cases, no such instructions for use are needed for a device if it can be used properly and safely without them."	
Product support contact details		Precautions or measures to be taken in the event of changes in the performance, or malfunction of the device, including a contact telephone number, if appropriate
Intended use		Intended use or purpose (e.g. monitoring, screening or diagnosis), including an indication that it is for in vitro diagnostic use
Test method essentials		Test principle, specimen type, conditions for collecting, handling and preparing the specimen
Sensitivity and specificity		Analytical performance characteristics, such as sensitivity, specificity, accuracy (a combination of trueness and precision) Diagnostic performance characteristics, such as sensitivity and specificity
Safe disposal information		Any precautions to be taken for disposal of the device or its accessories (e.g. lancets), any consumables used with it (e.g. batteries or reagents) or any potentially infectious substances of human or animal origin

References to Annex 7

1. European Commission. Directive 98_79_EC 27 Oct 1998 on in vitro diagnostic medical devices. Strasbourg, 1998.
<http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:31998L0079:en:html>
<http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CONSLEG:1998L0079:20031120:en:pdf>
2. Global Harmonization Task Force. Essential principles of safety and performance of medical devices.
<http://www.ghtf.org/documents/sg1/sg1n41r92005.pdf>

ANNEX 8

WHO product dossier for prequalification of diagnostics

The table of contents of the WHO *Instructions for compilation of a product dossier – prequalification of diagnostics (1)* lists the requirements for compiling a RDT product dossier. The ‘essential principles’ refer to the requirements for an in vitro diagnostic medical device, as expressed in a range of documents (e.g. 2).

1. Introduction
2. Intended audience
3. The product dossier
 - 3.1 About the product dossier
 - 3.2 Submission of a product dossier
4. Dossier format
 - 4.1 Dossier clarity
 - 4.2 Layout and order
 - 4.3 Language and units of measure
5. The product
 - 5.1 Regulatory versions of this product
 - 5.2 Product description including variants (configurations) and accessories
 - 5.3 Essential principles checklist
 - 5.4 Risk analysis and control summary
6. Design and manufacturing information
 - 6.1 Product design
 - 6.1.1 Design overview
 - 6.1.2 Formulation and composition
 - 6.1.3 Biological safety
 - 6.1.4 Documentation of design changes
 - 6.2 Manufacturing processes
 - 6.2.1 Overview of manufacture
 - 6.2.2 Sites of manufacture
 - 6.2.3 Key suppliers
7. Product performance specification and associated validation and verification studies
 - 7.1 Analytical studies
 - 7.1.1 Specimen type
 - 7.1.2 Analytical performance characteristics

- 7.1.2.1 Accuracy of measurement
 - 7.1.2.2 Analytical sensitivity
 - 7.1.2.3 Analytical specificity
 - 7.1.2.4 Metrological traceability of calibrators and control material values
 - 7.1.2.5 Measuring range of the assay
 - 7.1.2.6 Validation of assay cut-off
 - 7.2 Stability (excluding specimen stability)
 - 7.2.1 Claimed shelf-life
 - 7.2.2 In-use stability
 - 7.2.3 Shipping stability
 - 7.3 Software verification and validation
 - 7.4 Clinical evidence (clinical or diagnostic sensitivity and specificity)
 - 7.4.1 Clinical evaluation – Manufacturer
 - 7.4.2 Clinical evaluation – Independent study
 - 8. Labelling
 - 8.1 Labels
 - 8.2 Instructions for use
 - 9. Commercial history
 - 9.1 Countries of supply
 - 9.2 Adverse events and field safety corrective actions
 - 10. Regulatory history
 - 11. Quality management system
 - 11.1 Quality manual
 - 11.2 Quality management system documents
 - 11.3 Quality management system certification
 - 12. Contact information
 - 13. Reference documents
- Annex A. Essential principles checklist

References to Annex 8

1. *Instructions for compilation of a product dossier – prequalification of diagnostics*. Geneva, World Health Organization.
https://www.who.int/diagnostics_laboratory/evaluations/100506_pqdx_018_dossier_instructns_v1.pdf

ANNEX 9

ISO 13485: Medical devices quality management system

ISO 13485 is based on ISO 9001 requirements and specifies international standards for implementation of a quality management system by a manufacturing company. It covers both aspects related to human resources and requirements for the manufacturing facility (1). ISO/TR 14969 (2) is a technical report that provides guidance for the application of ISO 13485. Continuous monitoring and evaluation at each step of the cycle help to improve the system.

ISO certificate can be checked and verified on the web site of the certification body. The verification will have value if the certification body is accredited by the competent body for the country.

The relevant sections of ISO 13485 are listed below:

4. Quality management system
 - 4.1 General requirements
 - 4.2 Documentation requirements
5. Management responsibility
 - 5.1 Management commitment
 - 5.2 Customer focus
 - 5.3 Quality policy
 - 5.4 Planning
 - 5.5 Responsibility, authority and communication
 - 5.6 Management review
6. Resource management
 - 6.1 Provision of resources
 - 6.2 Human resources
 - 6.3 Infrastructure
 - 6.4 Work environment
7. Product realization
 - 7.1 Planning of product realization
 - 7.2 Customer-related processes
 - 7.3 Design and development
 - 7.4 Purchasing
 - 7.5 Production and service provision
 - 7.6 Control of monitoring and measuring devices
8. Measurement, analysis and improvement
 - 8.1 General
 - 8.2 Monitoring and measurement
 - 8.3 Control of nonconforming product
 - 8.4 Analysis of data
 - 8.5 Improvement

Risk management

ISO 13485:2003 requires risk management throughout product realization, up to use of the medical devices by health providers, as demonstrated by the inclusion of product delivery storage requirements in product realization. The manufacturer must determine the requirements specified by the customer, including those for delivery and post-delivery activities. They include requirements not stated by the customer but necessary for the specified or intended use, as well as statutory and regulatory requirements related to the product.

The standard for risk management is ISO 14971:2007 (3), which refers users of ISO 13485 to this standard for guidance.

Risk management covers:

- risk analysis,
- risk evaluation,
- risk control, and
- production and post-production information.

These elements should be described in the risk management plan established by the manufacturer and should become the documentary foundation for procurement risk management. Risk management is an integral part of the quality assurance system.

References to Annex 9

1. International Organization for Standardization. *ISO 13485:2003 Medical devices – quality management systems – Requirements for regulatory purposes*. Geneva.
2. International Organization for Standardization. *ISO/TR 14969:2004. Medical devices – quality management systems – guidance on the application of ISO 13485:2003*. Geneva.
3. International Organization for Standardization. *ISO 14971:2007 Medical devices – application of risk management to medical devices*. Geneva.

ANNEX 10

Lot-testing request form

Requests for more information on the lot-testing programme (1) can be obtained by sending the completed form below to WHO/FIND at: mal-rdt@wpro.who.int or info@finddiagnostics.org. An example of a lot-testing request form is shown below (from <http://www.wpro.who.int/NR/rdonlyres/AF9B4A67-3BD7-4406-8D19-BA8DA3F6405C/0/Samplelottestrequestform.pdf>).

TRANSPORT DETAILS

Requesting institution (institution or organization requesting testing)	
Sending institution (if different from the requesting institution)	
Date sent (dd/mm/yyyy)	

RDT DETAILS

RDT product name (as on product insert)	Manufacturer	Catalogue no.	Lot no.	Expiry date (dd/mm/yyyy)	Quantity provided	
					No. of boxes	No. of tests per box
(Delete or add rows as necessary.)						
Temperature monitor included in the shipment: ☐ Yes ☐ No (Not routinely included) If 'Yes', send the monitor with the RDTs to the testing institution (RDT quality control laboratory)						

TESTING DETAILS: The sending institution should insert the number of RDTs sent and an explanatory note in blank cells below if the number of RDTs sent differs from the number specified by prior agreement.

Minimum number of RDTs required per lot	The number of RDTs sent may be varied for non-routine testing. Discuss with the lot-testing coordinator and insert details below.
Pf-only RDTs: 125 tests	
Combination RDTs: 175 tests	
Additional comments from the requestor	

CONTACT DETAILS FOR RECEIPT OF RESULTS: (Delete or add columns as necessary.)

Name of contact person			
Position			
Institution and address			
Telephone and fax numbers			
e-mail address			

This form should be sent by e-mail, before sending the RDTs, to mal-rdt@wpro.who.int and the lot-testing coordinator or the e-mail contact specified on the WHO RDT web site (www.wpro.who.int/sites/rdt). Also include a hard copy with the RDTs. A summary of results will be published regularly, which will include the product name but not the procuring agency's name.

Reference to Annex 10

1. Form 2.02: Malaria RDT Lot-test Request Form. Manila, WHO Regional Office for the Western Pacific.
<http://www.wpro.who.int/NR/rdonlyres/AF9B4A67-3BD7-4406-8D19-BA8DA3F6405C/0/Samplelottestrequestform.pdf>

ANNEX 11

Lot-testing report form

The lot-testing centres follow procedures developed by WHO, and the initial results are usually returned within 5 working days. Retained RDTs are then monitored every 6 months throughout their shelf-life at close to the manufacturer's recommended maximum storage temperature. Results are reported to the procuring agency on a report form (1), an example of which is shown below (from <http://www.wpro.who.int/NR/rdonlyres/BC9BC2BA-4A77-4801-B8D1-ABFA22A7A1BB/0/LottestingQCreportresultform.pdf>).

MALARIA RAPID DIAGNOSTIC TEST

Quality control report
(Lot testing)

Report prepared by (name):	
Quality assurance RDT network laboratory (institute):	
Institution that requested the RDT quality control (name):	
Place from where tests were sent (institution, town, country):	
Contact:	
For the attention of (name):	
Date of report (dd/mm/yyyy):	

Interpretation of results: see last page

RDT product name (as per product insert):	
Catalogue no.:	
Manufacturer's name:	
Date received (dd/mm/yyyy):	
Place received:	
Transport method from sending institution to testing institution:	
Storage conditions during transport from sending institution to testing institution	
Condition of RDTs on receipt:	

KIT CONTENTS (please check box)

☐ Buffer	☐ Lancet	☐ Alcohol swab	☐ Blood transfer device
Other:			

Lot no.	Expiry date: dd/mm/yyyy or mm/yyyy	No. of boxes received	No. of tests per box	Testing interval	Result

Insert additional rows if necessary

SUMMARY OF RESULTS

Testing interval (months)	Temp. of storage (°C)	Date tested (dd/mm/yyyy)	Product (lot no.)						
			Result ■	% positive results △					Observations
				Pf 200	Pf 2000	Pv 200	Pv 500 •	Pv 2000	
Expand									
12									
6									
0									

Add new rows as necessary at time of reporting.

■ Result = 'Pass', 'Deferred', 'Fail'

△ % positive results: total percentage of RDTs giving a positive result for a given *Plasmodium* species (Pf, *P. falciparum*; Pv, *P. vivax*) at a given parasite density (200, 500 or 2000 parasites/μl).

• Delete if necessary

METHOD**1. Quality control testing**

RDTs were tested with frozen samples based on the algorithm described in SOP 2.06 of the WHO quality control methods manual for malaria RDTs. For a lot of RDTs to pass the quality control assessment, all dilutions must be positive (100%). RDTs that do not meet these criteria will be forwarded to a second laboratory for confirmation. False-positive results will be reported in the 'Observations' section.

The RDT lots will be retained in this laboratory for long-term quality control. A further report will be issued after the next quality control assessment.

2. Samples used for quality control testing

Quality control samples of dilutions from wild-type parasites prepared according to SOP 3.08 of the WHO quality assurance methods manual for malaria RDTs (3). Samples are stored at -70°C.

Samples used include:

- Negative control: 0 parasites/μl of *Plasmodium* spp.
- Low positive control: 200 parasites/μl of *P. falciparum*
- High positive control: 2000 parasites/μl of *P. falciparum*
- Low positive control: 200 parasites/μl of *P. vivax**
- Medium positive control: 500 parasites/μl of *P. vivax**
- High positive control: 2000 parasites/μl of *P. vivax**

* Delete as necessary

3. RDT preparation method

RDTs were tested as per the manufacturer's instructions, with a micropipette used for blood transfer.

Details of RDT quality control testing results: ☐ month of testing

EXAMPLES OF RESULTS TABLES. USE ONLY ONE TABLE. TABLE CAN BE EXTENDED TO INCLUDE MULTIPLE LOTS OF THE SAME PRODUCT. (ALWAYS USE A DIFFERENT REPORT FORM FOR EACH DIFFERENT PRODUCT.)

TABLE 1. INITIAL TESTING (delete for interval testing)

Quality control dilution		Product (lot)		
Sample	Parasites/μl	No. tested	No. positive	% positive
Pf	200	6		
	2000	1		
Pf	200	6		
	2000	1		
Pf	200	6		
	2000	1		
Pf	200	6		
	2000	1		
Pv	200 or 500*	6		
	2000	1		
Pv	200 or 500*	6		
	2000	1		
Pv	200 or 500*	6		
	2000	1		
Pv	200 or 500*	6		
	2000	1		
		No. tested	No. negative	% negative
Negative control List sample IDs	0	10		

* Delete as necessary, add additional row if both 200 and 500 dilutions are used.

TABLE 1A. INTERVAL TESTING (delete for initial testing)

Quality control dilution		Product (lot)		
Sample	Parasites/μl	No. tested	No. positive	% positive
Pf	200	2		
	2000	1		
Pf	200	2		
	2000	1		
Pv	200 or 500*	2		
	2000	1		
Pv	200 or 500*	2		
	2000	1		
		No. tested	No. negative	% negative
Negative control List sample IDs	0	2		

TABLE 2. REPEAT TESTING WITH DIFFERENT QUALITY CONTROL PANELS

Quality control dilution		Product (lot)		
Sample	Parasites/μl	No. tested	No. positive	% positive
Pf	200	6 (initial), 2 (interval)		
	2000	1		
Pf	200	6 (initial), 2 (interval)		
	2000	1		
Pv	200 or 500*	6 (initial), 2 (interval)		
	2000	1		
Pv	200 or 500*	6 (initial), 2 (interval)		
	2000	1		
		No. tested	No. negative	% negative
Negative control List sample IDs	0	1		

* Delete as necessary; add additional row if both 200 and 500 dilutions are used.

TABLE 3. REPEAT TESTING OF QUALITY CONTROL SAMPLES AGAINST STOCK RDTs TO ENSURE QUALITY CONTROL SAMPLE INTEGRITY

Quality control dilution		Product (lot)		
Sample	Parasites/μl	No. tested	No. positive	% positive
Pf	200	2		
	2000	1		
Pf	200	2		
	2000	1		
Pv	200 or 500*	2		
	2000	1		
Pv	200 or 500*	2		
	2000	1		
		No. tested	No. negative	% negative
Negative control List sample IDs	0	1		

* Delete as necessary; add additional row if both 200 and 500 dilutions are used.

Delete tables 2 and 3 if not used, and delete Pv sections if not applicable.

4. INTERPRETATION OF RESULTS

In order for a lot of RDTs to pass a quality control assessment, all the quality control dilutions must be positive (100%). Performance on *Plasmodium*-negative control samples should also be taken into account in interpreting results

Interpretation of results:

- *Pass*: This RDT lot passed the quality control test, and the RDT sample assessed detects antigen at a threshold *sufficient for use* in the field.
- *Deferred*: This RDT lot failed the assessment and has been sent to another institution for confirmation. A final report will be issued on receipt of the confirmatory results. It is recommended that the lot be *retained* until a final report is received.
- *Fail*: This RDT lot failed the initial quality control assessment and also failed confirmatory testing at another institution. It is recommended that this lot *not be used* in the field, as it has been assessed as lacking sufficient sensitivity. It is recommended that the manufacturer be contacted and advised of the results.

Note: This RDT lot will be retained for long-term quality control. A further report will be issued only after the next scheduled assessment (6 months).

“This assessment is performed in collaboration with the World Health Organization, the Foundation for Innovative New Diagnostics and the Special Programme for Research & Training in Tropical Diseases. The report is prepared for the confidential information of the institution that submitted the rapid diagnostic tests (RDT) for assessment. The results are for use of the institution that submitted the RDTs for assessment as evidence that the stored samples of the particular lot of RDTs tested performed with sufficient sensitivity for use. They must not be used for purposes of advertising or otherwise promoting a product, or as evidence of formal approval or recommendation of a product, without the written permission of the testing institution and World Health Organization. Other than confirmation of sufficient sensitivity of the sample of the tested lot, the results listed here do not indicate endorsement of the RDT product by the World Health Organization or the testing institution. While the results indicate that the RDTs tested detect antigen to an acceptable threshold in the quality control parasite samples used for testing, they do not necessarily reflect actual sensitivity in the field where local storage conditions, variation in parasite antigen and host factors may affect operation. Recommendations on use and storage of RDTs in the field can be obtained from the WHO web site <http://www.wpro.who.int/rdt>, or by e-mail from mal-rdt@wpro.who.int.”

Signed:
Technician
Laboratory head

Copies of report

Include e-mail copy to: Requesting Institution
WHO-FIND lot-testing coordinator

Hard copy to be retained by testing institute

Reference to Annex 11

1. *Malaria rapid diagnostic test: quality control report*. Manila, WHO Regional Office for the Western Pacific.
http://www.wpro.who.int/NR/rdonlyres/BC9BC2BA-4A77-4801-B8D1-ABFA22A7A1BB/0Lot_testingQCreportresultform.pdf.90

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