WHO product testing round 5

WHO-FIND Malaria RDT Evaluation Programme

Information for manufacturers and procurers on progress towards product testing of malaria rapid diagnostic tests.

Four previous rounds of testing have been completed since 2008 and Round 4 results were published in December 2012. Together these results add to existing comprehensive guidance on the potential performance characteristics of malaria RDTs to national malaria control programmes and other major procuring agencies.

Round 5 of the WHO Product Testing Programme started in January 2013, and requests for participation in Round 5 were submitted to WHO by 24 September 2012. All information regarding Product Testing Round 5 is listed on this page.

This document compiles all the steps followed during this process with all related letters, documents and supporting materials.

For more information concerning the other rounds, please see:

Round 1 | Round 2 | Round 3 | Round 4

For more information on the WHO-FIND Malaria RDT Evaluation Programme, please see:

http://www.who.int/malaria/areas/diagnosis/rapid-diagnostic-tests
16 August 2012 - Seeking expression of interest in participating in the WHO malaria RDT product testing programme

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- Malaria rapid diagnostic test performance. Results of WHO product testing of malaria RDTs: Round 5 (2013)
- Summary results of WHO product testing of malaria RDTs: Round 1-5 (2008-2013)
Dear Sir/Madam,

**WHO Malaria Rapid Diagnostic Test (RDT) Product Testing Programme**

The World Health Organization (WHO) is exploring the interest of your company to participate in the Fifth Round of the WHO Malaria RDT Product Testing Programme to commence in January 2013.

The proposed RDT evaluation, coordinated by WHO/GMP (Global Malaria Programme) and the Foundation for Innovative New Diagnostics (FIND), aims to evaluate commercially available, rapid simple point-of-care antigen-detecting diagnostics for malaria that are appropriate for use in primary health care settings in developing countries. The results of the past three rounds of product testing have been published annually since 2008 and preparation of the Round 4 of product testing is currently underway.

Results of the product testing form the basis of WHO procurement recommendations and tendering for WHO procurement. As with past Rounds, products accepted into the WHO Malaria RDT Product Testing Programme will be listed on the WHO Malaria RDT web site: http://www.wpro.who.int/sites/rdt/home.htm

WHO is currently only seeking an Expression of Interest (EOI) for participation in the upcoming Round 5 of the Product Testing Programme. This EOI, which must include an indication and description of the product(s) proposed for evaluation, should be submitted in the format of Form 1 attached to this document. This must be received electronically and followed by hard copy by WHO by **24 September 2012** at the address mentioned in Annex 1.

Although the submission of an EOI will not be binding on either party, the submission is required by 24 September 2012 for inclusion of each product in the Product Testing Programme. Depending on the number of products submitted for inclusion, manufacturers may be restricted to 2 or 3 of the products submitted in the Expression of Interest.

ENCLS: (as stated)
A subset of the product test panel prepared from cultured *P. falciparum* malaria parasites will be made available to manufacturers for their own quality control in October 2012, prior to the final submission of products to the Product Testing Programme, if they wish to test products against this panel prior to submission.

In order for a product to be published in the ‘Summary Results of Rounds 1-5’ document and published on the WHO and FIND websites, and to be eligible for WHO procurement, manufacturers are now required to resubmit products within less than 5 years. Therefore, any manufacturer who submitted products to Round 1 (2008), who has not already resubmitted products to future rounds (Rounds 2,3,4), and wants to continue to be listed in the Product Testing Report and be eligible for WHO procurement must participate in Round 5. A list of manufacturers and products affected by this policy is included in Annex 3.

Voluntary resubmission of products (from Rounds 2,3,4) is still acceptable and as in previous years, the results of earlier rounds will be replaced in the performance report by results of subsequent rounds to which the product is submitted. It is noted that tests targeting *P. falciparum* pLDH are not well represented in previous rounds of product testing, and manufacturers are encouraged to consider submitting such tests. However, target antigen will not be a factor in decision by WHO and FIND on final product inclusion.

Further details of the WHO Malaria RDT Product Testing Programme are provided in the enclosed information documents and application forms.

| Annex 1 General information on the Programme and timelines |
| Annex 2 Definition of ‘Product’ and ‘Lot’ |
| Annex 3 Requirements for resubmission: Product List |
| Annex 4 Information on internal heat stability protocol |
| Form 1 Expression of Interest (EOI) |
| Form 2 Material Transfer Agreement/Confidentiality Agreement |
| Form 3 Final product list |
| Form 4 Joint-submission or joint-listing of products |

If your company wishes to submit products for consideration for inclusion in Round 5 of the WHO Malaria RDT Product Testing Programme, please read the enclosed documents carefully and submit the required EOI within the permitted time-frame.

We look forward to receiving your company's EOI by 24 September 2012. In the meantime, you can obtain additional information on the Product Testing Programme by visiting the website: [http://www2.wpro.who.int/sites/rdt/who_rdt_evaluation/call_for_testing_round5.htm](http://www2.wpro.who.int/sites/rdt/who_rdt_evaluation/call_for_testing_round5.htm) and/or by sending an email to: Malaria_rdt@who.int

Yours sincerely,

David Bell  
Head of Programme  
Malaria and Acute Febrile Syndrome  
Foundation for Innovative New Diagnostics (FIND)  

Robert Newman  
Director  
Global Malaria Programme  
World Health Organization
GENERAL INFORMATION ON PROGRAMME AND TIMELINES: ROUND 5

This document includes details of Round 5 of World Health Organization (WHO) Malaria Rapid Diagnostic Test (RDT) Product Testing and criteria for inclusion of products. The Malaria RDT Product Testing Programme is a collaboration of the WHO Global Malaria Programme (GMP), the Foundation for Innovative New Diagnostics (FIND) and the US Centers for Disease Control and Prevention (CDC).

The only action necessary now for a manufacturer interested in participating in Round 5 WHO Product Testing is to send the details of all products considered for submission in accordance with the instructions described below. Such an Expression of Interest will not be binding on either party, but must be received electronically by WHO by 24 September 2012 to enable submission of the listed products in the fifth round of testing (which is scheduled to commence at the end of January of 2013).

A. Introduction

WHO is proposing to undertake another round of evaluations to assess the performance of antigen-detecting malaria rapid diagnostic tests (RDT). All product testing will be conducted at the Malaria Branch, Division of Parasitic Diseases, and Centers for Disease Control and Prevention, Atlanta, U.S.A., in collaboration with the Foundation for Innovative New Diagnostics (FIND), with an optional stability assessment performed at the site of manufacture.

1. A total of 2200 Malaria RDTs, consisting of 1100 tests and standard kit contents, from each of two separate lots of each product, will be required to be submitted to the Programme. Testing will be conducted in two phases. Phase 1 of the testing process will be performed against a panel of cryo-preserved preparations of cultured *P. falciparum* parasites and 20 clean-negative samples. Phase 2 will be performed against a panel containing diluted cryo-preserved preparations of wild parasites (*P. falciparum* and *P. vivax*), and parasite-negative samples. Products that have previously achieved the WHO procurement criteria will not be required to be tested in Phase 1 of the product testing programme. Manufacturers are responsible for the RDT and courier costs and any other associated costs of transport of RDTs to US CDC.

2. Manufacturers have the option to obtain a subset of the product testing panel prepared from cultured *P. falciparum* malaria parasites for their own quality control testing prior to submission of products to the WHO Product Testing Programme, and for stability testing at the manufacturing site. There is no charge for this panel but manufacturers are responsible for the courier costs (from CDC to the manufacturing site) and any associated costs of transport and importation.

3. The opportunity for submissions of request for inclusion of products (Expression of Interest, EOI) in Round 5 of WHO Product Testing will close on 24 September 2012. Only products listed on the Form 1 of the submission will be eligible for Round 5. WHO reserves the right to later limit the number of products per manufacturer if the total number of products in the EOI is beyond the capacity for testing by the Programme in a single round of Product Testing. In past rounds, this number has been restricted to 2 or 3 products.

4. The WHO Malaria RDT Product Testing Programme will publish the list of products and associated performance data in various formats including: i) a dedicated WHO website page ii) electronic and hard copy of Round 5 results iii) electronic and hard copy of compiled Rounds 1-5 results. In advance of all publications, manufacturers will be informed of the performance results, in accordance with the terms of the attached sample Confidentiality Agreement. (The Confidentiality Agreement in Form 2 should not be signed at this stage, but will be required at the time of final product submission for the WHO Malaria RDT Product Testing Programme – see diagram on page 6).
5. As with previous WHO Product Testing rounds, results of Round 5 will form the basis of procurement recommendations of WHO and the WHO tendering programme and will guide future procurement of RDTs by WHO, other UN Agencies and national health authorities. Publication of data on product performance and/or inclusion in the above mentioned website list does not guarantee that the RDTs in question will actually be procured by WHO or any other party.

6. In order for a product to be published in the ‘Summary Results of Rounds 1-5’ document and published on the WHO and FIND websites, and to be eligible for WHO procurement, manufacturers are now required to resubmit within less than 5 years. Therefore, any manufacturer who submitted products to Round 1 (2008), who has not already resubmitted products to future rounds (Rounds 2,3,4), and wants to continue to be listed in the Product Testing Report and be eligible for WHO procurement, must participate in Round 5. A list of manufacturers and products affected by this policy is included in Annex 3.

Voluntary resubmission of products (from Rounds 2,3,4) is still acceptable and as in previous years, the results of earlier rounds will be replaced in the performance report by results of subsequent rounds to which the product is submitted.

7. The manufacturer of a listed product for which the product specifications, as outlined in Annex 2, have been changed, is requested to inform WHO of such changes prior to the commercial release of the changed product. WHO may remove a product from the website list or require re-submission of a product for performance testing if changes in product specifications indicate that the RDT should be considered a new product, or performance data obtained from WHO-FIND lot testing services in the field are considered to be consistently outside those of the product testing programme published by WHO.

8. The list of submitted products does not in any way imply an endorsement, certification, warranty of fitness or recommendation by WHO of any company or product for any purpose, and does not imply preference over products of a similar nature that are not mentioned. WHO furthermore does not warrant that: (1) the list is complete and/or error free; and/or that (2) the products listed are of acceptable quality, have obtained regulatory approval in any country, or that their use is otherwise in accordance with the national laws and regulations of any country, including but not limited to patent laws. Inclusion in the list does not furthermore imply any approval by WHO of the products in question (which is the sole prerogative of national authorities).

9. Participation in WHO Malaria RDT Product Testing and publication by WHO of the testing results may not be used by the manufacturers and suppliers concerned for commercial or promotional purposes. With respect to the manufacturers' or suppliers' participation in the Product Testing Programme, under no circumstances is a manufacturer or supplier authorized to refer to WHO and/or FIND, the publication of the testing results by WHO and/or FIND and/or inclusion in the website list, in any statement or material of an advertising or promotional nature, press release and/or similar public statement and/or other material aimed at promoting the manufacturer or supplier and/or its products.

B. Criteria for entry to the WHO Malaria RDT Product Testing Programme and Timelines

Conditions of entry are derived from the recommendations of WHO expert consultations at Geneva, Kisumu and Atlanta in 2006, and confirmation in subsequent consultations of the WHO-FIND Malaria RDT Evaluation Programme Steering Committee (formerly referred to as the Malaria RDT Specimen Bank Review Committee). Conditions for testing of products as part of the WHO Malaria RDT Product Testing Programme¹ (see Diagram on page 6)

¹ It is planned to include a product specific audit as a criteria in the future, through a mechanism to be determined by WHO
1. **By 24 September 2012:** Submission of an Expression of Interest (EOI) to WHO (as in the attached Form 1).

   Documents to be submitted by E-mail (scanned copies) and hard copy to:

   Izabella Suder-Dayao  
   WHO/TDR  
   20 Appia Avenue  
   1211 Geneva  
   Switzerland  
   Tel: +41 (22) 791 2261  
   Fax: +41 (22) 791 4854  
   E-mail: suderi@who.int  

   With a copy to Malaria_rdt@who.int

2. **By 2 November 2012** (if EOI is accepted) all items listed below must be received by e-mail as scanned copies. Hard copies must follow by courier.: Fulfillments of the requirements for taking part in Round 5 of WHO Product Testing includes:

   **NB: Do not send the below documents before notification by WHO of acceptance of products listed in Form I.**

   a) Valid ISO 13485:2003 from all sites where the product(s) is manufactured

   b) Provision of an acceptable heat stability protocol of internal quality assurance (ANNEX 4).

   c) Submission of 2 original signed copies of the Confidentiality Agreement (Form 2) and acceptance of conditions for product testing and publication of results.

   d) Final Product List (Form 3)

   e) Product leaflets/package insert

   **Please ensure that product leaflets sent by email, hard copy and accompanying the RDT shipment are accurate and identical. In the case of any discrepancies, the leaflets/instructions accompanying the RDT shipment will apply.**

3. **By close of business (COB) 14 January 2013:** Delivery of Malaria RDTs to US CDC, Atlanta. (see point E below) at manufacturer’s cost

4. **Re-labeled products that are manufactured at the same site and under the same conditions as a tested product, and fulfill the criteria in Form 4, may be jointly listed with the tested product under the criteria and conditions listed in Form 4.**

   The above actions should be undertaken if and when WHO or FIND so notifies the manufacturer. No product testing will take place unless the manufacturer has fulfilled the above conditions by the dates set by WHO and FIND and in accordance with WHO and FIND's instructions.
**ANNEX 1**

**C. Supply of products for testing**

- A total of 2200 tests consisting of 1100 tests, and standard contents, from each of the two separate lots must be submitted to the US CDC, Atlanta, according to instructions provided by WHO and/or FIND.

- All RDTs must be received at US CDC by COB 14 January 2013 in order to be accepted for product testing. (Temperature monitors for the duration of the transportation can be obtained from WHO free of charge at request)

- All products will be stored in an air conditioned, temperature monitored room from the time of receipt until the actual testing occurs (the product testing site will determine the order in which testing will be conducted)

- If a product does not display sufficient performance against the Phase 1 panel, the lot will not be tested against the Phase 2 panel. Sufficient performance is defined as \( \geq 80\% \) panel detection score against 2000 parasites/\( \mu l \) samples, with \( \leq 25\% \) false positive rate against 20 clean-negative samples.

**Important note on RDT format**

Manufacturers may submit commercially-available antigen-detecting lateral flow products in any format and for any target antigen. RDTs with the same product name but different format (e.g. cassette and dipstick) are considered as separate products and will require separate submission and testing. Results are interpreted through visual reading. On publication of the testing results, the introductory text accompanying the table of product performance characteristics will emphasize the current WHO recommendation that cassettes are preferred to dipsticks for field use in endemic countries. Manufacturers are therefore advised to consider submitting only tests in cassette format.

It is noted that previous Rounds of WHO Malaria RDT Product Testing have evaluated few products targeting *P. falciparum*-specific pLDH. These products may have advantages in certain endemic settings and therefore, we encourage manufacturers to seriously consider submission of such products.

**D. Oversight:**

The WHO Malaria Specimen Bank (currently at US CDC), is the repository of characterized samples against which product testing will occur, and includes culture-derived and wild-type malaria parasites, and parasite negative samples. The wild-type parasites are collected from a geographically-diverse network of collection sites in Asia, Africa and South America, and prepared according to standard protocols.\(^2\)

The WHO-FIND Malaria RDT Evaluation Programme Steering Committee (formerly referred to as the Malaria RDT Specimen Bank Review Committee) oversees the technical and logistical aspects of the testing and evaluation process, including the development of Standard Operating Procedures (SOPs), oversight of ethical approval for the collection sites contributing to the Specimen Bank (including submission to the WHO Ethics Committee, and local ethical review board) and oversight of the product testing and reporting of results.

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Terms of Reference of the WHO-FIND Malaria RDT Evaluation Programme Steering Committee

The WHO-FIND Malaria RDT Evaluation Programme Steering Committee (formerly referred to as the Malaria RDT Specimen Bank Review Committee) will provide recommendations to WHO and FIND on:

- Development and modifications of SOPs for specimen collection and use
- Collection, characterization and maintenance of the Specimen Bank
- Policy on access to the Specimen Bank
- Protocols for laboratory-based testing of the accuracy and stability of malaria RDTs, including product testing and lot testing
- Review and interpretation of the results of product testing, prior to publication.

Composition

Core:

- WHO/GMP [2] (as of 1 July 2012)
- Foundation for Innovative New Diagnostics (FIND) [2]
- US Centers for Disease Control and Prevention (CDC) [2]
- Médecins sans Frontières [1]
- Collection sites: 1 African [1]
- 1 non-African [1]
- Specimen characterization centers:
  - Hospital for Tropical Disease, UK [1]
  - Army Malaria Institute, AU [1]
Step 1: Submission of Expression of Interest (Form 1 +/- Form 4)

Step 2: WHO-FIND sends EOI Acceptance letter to manufacturers, final number of tests per manufacturers that can be submitted to Round 4 and instructions for obtaining the optional culture panel from CDC for manufacturer quality control testing.

Step 3:
  i) Submission of ISO 13485:2003 from ALL manufacturing sites and provision of heat stability protocol of internal quality assurance (see Annex 4)
  ii) TWO signed ORIGINAL copies of Confidentiality Agreements (Form 2)
  iii) Final list of products (Form 3)
  iv) Corresponding product inserts/leaflets for each product submitted.
  v) OPTIONAL - Request for temperature monitor for duration of RDT transport

Step 4: Review of the submissions by Steering committee

Step 5: WHO sends Confirmation of Acceptance of Final list of products for the Product Testing Programme

Step 6: Applicant submits a total of 2200 tests and standard kit contents consisting of 1100 tests from each of two separate lots to US CDC

Step 7: Applicants optionally request and obtain parasite specimen samples from US CDC for the stability testing at manufacturer site

Step 8: Applicant optionally submits results of the stability test performed at the manufacturer site every 3 monthly until the end of the specified shelf life.

Step 9: Manufacturers reports with product specific results released to applicants.

Step 9: WHO-FIND Publication of Round 5 and compiled Rounds 1-5 Product Testing Results

Deadline for Receipt
24 September 2012

5 October 2012

Deadline for Receipt
2 November 2012

November 2012

8 November 2012

February 2013

February-March 2014

April-May 2014
E. Further Information

Further information on the Product Testing Programme can be found in:


All the above documents can be found at: http://www.wpro.who.int/sites/rdt/documents/list.htm; www.finddiagnostics.org and www.who.int/tdr or can be obtained by sending an email to: Malaria_rdt@who.int
DEFINITION OF A 'PRODUCT' AND 'LOT'

It is necessary to clearly define the terms “product” and “lot” to implement the proposed testing scheme, as product testing results should be applied only to a specifically defined and labelled product, and lot testing results should be applied only to a clearly defined and labelled lot.

(1) **Lot.** The definition of a “lot” is the responsibility of the manufacturer. All manufacturers must have current ISO 13485:2003 or US FDA 21 CFR 820 certification and an appropriate “lot” definition must be compatible with this.

(2) **Product.** Defining a malaria RDT “product” for the purposes of a product testing scheme is more difficult. However, this definition should be based on consistency in overall design and on the major constituents of the RDT that are likely to have a significant impact on RDT stability and accuracy. Assuming that evidence of equivalent performance can be provided, the following applies:

a) Similar but re-labelled products from various manufacturers should generally be considered different products (see joint listing of products below) but may be considered the same product if specifically indicated by the manufacturers concerned.

b) **Monoclonal antibodies (Mab)** – A change in target epitope, or of the species from which target antigen for Mab development is derived, should constitute a new product. A change in source (manufacturer) or modifying the amount of Mab used in a test would not constitute a new product if the Mab cell line originated from the same source.

c) **Dye conjugate** (signal reagent) – A change in specification or type of label (e.g. colloidal gold, latex particle or liposome) should constitute a new product, but a change in manufacturer/source should not.

d) **Format** – A change in assay presentation between, for example, a dipstick, cassette or card, constitutes a new product.

e) **Buffer** – A change in assay buffer constituents or pH does not constitute a new product.

(3) **Equivalence of performance.** Where changes made have the potential to significantly affect accuracy of the RDT, including changes in raw materials or components, including Mabs, signal reagents, buffers, nitrocellulose membranes, or in cassette design, equivalence of performance data should be provided to WHO to demonstrate that the modified product has a performance equivalent to, or better than, that previously submitted to formal testing. As this is an activity that should be performed as part of routine internal QA by the manufacturer, demonstration and notification of equivalence should not result in additional costs or workload.

Reference:

1. Towards Quality Testing of Malaria RDT-Evidence and Methods, 2006, World Health Organization
## REQUIREMENTS FOR RESUBMISSION: PRODUCT LIST

The following products have not been evaluated within the last 5 years and must resubmitted to Round 5 in order to continue to be listed in the Summary of WHO Malaria RDT Product Testing (Rounds 1-5) and considered for WHO tendering and procurement.

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>Product</th>
<th>Catalogue #</th>
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<tbody>
<tr>
<td>Access Bio, Inc.</td>
<td>CareStart Malaria pLDH (PAN)</td>
<td>G0111</td>
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<td></td>
<td>CareStart Malaria HRP2/pLDH (Pf/PAN) COMBO</td>
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<td>CareStart Malaria HRP2 (Pf)</td>
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<td>Acon Laboratories, Inc.</td>
<td>Malaria Plasmodium falciparum Rapid Test Device (Whole Blood)</td>
<td>IMA-402</td>
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<tr>
<td>Amgenix International, Inc.</td>
<td>OnSight - ParaQuick (Pan, Pf) Test</td>
<td>536-25DB</td>
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<tr>
<td>Biosynex</td>
<td>Immunoquick Malaria Falciparum</td>
<td>0502_K25</td>
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<td>Immunoquick Malaria +4</td>
<td>0506_K25</td>
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<td>Diagnostics Automation/Cortez Diagnostics Inc.</td>
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<td>172110P-25</td>
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<td>Human GmbH</td>
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<td>Hexagon Malaria Combi</td>
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<td>IND Diagnostic Inc.</td>
<td>One Step Malaria Antigen Strip</td>
<td>820-1</td>
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<td>Innovatek Medical Inc.</td>
<td>Quickstick Malaria Antigen Test(^2)</td>
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<td>Intec Products, Inc.</td>
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<td>Premier Medical Corporation Ltd.</td>
<td>First Response Malaria Ag HRP2</td>
<td>II3FRC30</td>
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<td>Span Diagnostics</td>
<td>Parahit-Total Device Rapid Test for (P. falciparum) and Pan malaria species</td>
<td>25989</td>
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<tr>
<td>Standard Diagnostics (^1)</td>
<td>SD Bioline Malaria Ag Pf</td>
<td>05FK50 (02-4)</td>
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<td>Unimed International</td>
<td>FirstSign – Malaria Pf Card Test</td>
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<tr>
<td></td>
<td>FirstSign – ParaView-2 (Pv + Pf) Card Test</td>
<td>2102CB-25</td>
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\(^1\) Alere companies

\(^2\) Co-listed with IND Diagnostics - One Step Malaria Antigen Strip (820-1)
INTERNAL HEAT STABILITY PROTOCOL AT MANUFACTURING SITE

As evidence of stability testing, WHO will accept protocols submitted by manufacturers that comply with the points listed below. However, based on the recommendations of the WHO Malaria Specimen Bank Committee in February 2010 (Bangkok, Thailand), WHO will continue to supply manufacturers participating in WHO Product Testing with cultured parasites but manufacturers are no longer required to submit results of stability testing to WHO.

The following standards for stability testing are modified from Hornback, L.A., originally published in IVD Technology, April 2004 (See references)

A stability study for in-vitro diagnostic device (IVD) reagents has the same elements as those dictated for stability testing of drugs including the following:

- A written stability testing programme designed to assess the stability characteristics of IVDs.
- A stability protocol with predefined acceptance criteria that can be correlated to the label claims.
- Testing multiple unique product lots. A stability study is required to use three product lots that are manufactured when the manufacturing process has been well defined and can be consistently executed.
- Evaluation of each stability attribute via a statistically valid sample size and testing intervals. The sample size should be sufficient to overcome the precision of the test method used, considering the cumulative effect of all elements of the test system (i.e., individual reagents and instruments). The test intervals should be chosen so that trends may be discerned from variability of the data. At a minimum, stability testing should continue to one time interval past labeled expiration.
- Control of material storage. For real-time stability testing, the IVD reagents should be stored under the conditions stated on the label (e.g., temperature, humidity, light protection).
- Testing IVD in the same container-closure system as the marketed product.
- Use of reliable, meaningful and specific test methods.

The requirement set forth in the last bullet point implies the use of blood samples containing adequate parasite antigen to produce a clear test line on the RDT near the minimum equivalent parasite density that the RDT is expected to detect.

Use of Accelerated Study Data

Accelerated stability studies are useful for predicting the shelf life of IVD. Such accelerated studies subject IVD to extreme conditions—typically elevated temperatures—to the extent that the device endures significant and measurable deterioration during the testing period. Mathematical extrapolations, such as the Arrhenius equation, are then used to calculate the predicted shelf life of the IVD. However, not all IVD follow a predictable degradation rate. Some products will perform acceptably until they fail, in which case only real-time testing will suffice.

According to the United States Food and Drug Administration's Office of In Vitro Diagnostic Device Evaluation and Safety, accelerated stability studies are acceptable in the following situations:

- establishing preliminary claims in new products only if there is sufficient correlation to an existing product and,
- supporting implementation of a change to an existing product.
ANNEX 4

The European standard EN 13640:2000 provides guidance on not only conducting real-time and accelerated stability studies but also making calculations using the Arrhenius equation. Only real-time stability data are acceptable for testing of either newly licensed IVD or major changes to existing IVD.

References

EXPRESSION OF INTEREST – NOTIFICATION OF INTEREST TO SUBMIT AN ANTIGEN- DETECTING MALARIA RAPID DIAGNOSTIC TEST TO THE WHO MALARIA RDT PRODUCT TESTING PROGRAMME

<table>
<thead>
<tr>
<th>Company name</th>
<th>Product Name¹</th>
<th>Catalogue Number</th>
<th>Plasmodium species targeted²</th>
<th>Target antigen(s)</th>
<th>Format³</th>
<th>Packaging (Individual or bulk)</th>
<th>Number of tests per box</th>
<th>All materials can be included? (lancets, swabs, wells if required)</th>
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</tr>
</tbody>
</table>
FORM 1

1. Write precisely how it should appear in all WHO publications, include ™ or ®, etc
3. 'Dipstick' refers to simple nitrocellulose strip which requires placement in well. Cassette / card indicates strip enclosed in (plastic) cassette or card.

Signature_______________________   Name _____________________________   Designation / position _________________________

NOTES:

• Please note that the information submitted on this form should be accurate for WHO publication purposes
• This Expression of Interest should be submitted to Izabela Suder-Dayao, WHO/TDR 20 Appia Avenue, Geneva 1211 Switzerland. Email: suderi@who.int, with an e-copy to: Malaria_rdt@who.int, by 24 September 2012.

<table>
<thead>
<tr>
<th>Product name</th>
<th>Shelf life</th>
<th>Storage temperature recommended by manufacturer</th>
<th>Temperature stability data on which shelf-life is based ('Accelerated' or 'Real time')</th>
<th>Contact person (If appropriate)</th>
<th>Address (for procuring tests)</th>
<th>Email URL</th>
<th>Contact numbers</th>
</tr>
</thead>
</table>
• Manufacturers should ensure that receipt is acknowledged. The provision of the required product details in this table, and the provision of evidence demonstrating compliance with the requirements set forth in Annex 1, is necessary in order for the products to be considered by WHO for inclusion in Round 5 of WHO Malaria RDT Product Testing.

• Only products listed above may be included in the list of products finally submitted to the Product Testing Programme. WHO reserves the right to limit the maximum number of products that can be submitted by manufacturers, if the listed products in the EOI is beyond the capacity for testing by the Programme in a single round of Product Testing. Manufacturer will be notified accordingly.

• If co-listing any product, Form 4 must also be completed and submitted with the EOI.

• WHO-FIND will notify a manufacturer if products have been accepted for this round of Product Testing Programme by 24 September, 2012.

• The submission of an EOI and/or the aforesaid evidence will neither obligate WHO to accept, nor obligate the manufacturer to actually provide, the listed products for product testing.

<table>
<thead>
<tr>
<th>CHECKLIST for manufacturer before Submission of EOI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Completed and signed product specifics (Form 1) – 24 September 2012 ☐</td>
</tr>
<tr>
<td>2. Completed and signed Co-listing details (if relevant) (Form 4) - 24 Sept. 2012 (signed by both the manufacturer and the owner of the product) ☐</td>
</tr>
</tbody>
</table>
WHO STANDARD CONFIDENTIALITY AND
MATERIAL TRANSFER AGREEMENT

Between

.........................................................………………having its principal offices at………………………………

.........................................................………………………………(hereinafter referred to as “the Company”);

and

The World Health Organization, Avenue Appia, 1211 Geneva 27, Switzerland, (hereinafter referred to as “WHO”).

The Company has developed (a) rapid malaria diagnostic test(s), known under the trademark :

…………………………………………………………………………………………………………
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which test(s) is/are further described in Exhibit 1 attached hereto, (hereinafter referred to as “the Product(s)”, and information relating thereto (hereinafter referred as the “the Information”). WHO is interested in having the Product(s) evaluated and tested in the WHO-FIND Malaria Rapid Diagnostic Test (RDT) Product Testing Programme, jointly coordinated by the WHO and the Foundation for Innovative New Diagnostics (FIND) hereinafter referred to as "WHO Malaria Rapid Diagnostic Test (RDT) Product Testing Programme".

Therefore, the Parties have agreed as follows:

(1) The Company shall disclose and furnish to WHO the Information and sufficient quantities of the Product(s) in order to enable WHO to assess the Information and arrange for such evaluations of the Product(s), as WHO may determine, are reasonably necessary to assess the performance of the Product(s) and its/their suitability for use at the primary health care settings in developing countries. At the conclusion of the testing and evaluation process, WHO will report the results thereof to the Company and, at the Company’s request and cost, return or destroy the
Information and any unused quantities of the Product(s). For the avoidance of doubt, "Information" as used herein does not include the data and information resulting from the testing and evaluation process (including the stability test(s) performed by the Company and submitted to WHO as part of the Product Testing Programme), any other testing results and the reports generated as a result of this Agreement (all the foregoing hereinafter jointly referred to as "the Testing Results"). Such Testing Results shall belong to WHO (subject always, however, to the other provisions of this Agreement).

(2) If and to the extent that the Information has been marked by the Company as "Confidential", WHO shall treat such Information as confidential and proprietary for a period of five years after disclosure to it. In this connection, WHO shall take all reasonable measures to ensure that the Information in question is not used for any purpose other than the aforementioned evaluation and testing activities and is not disclosed or provided to any person who is not bound by similar obligations of confidentiality and restrictions on use as contained in this Agreement.

(3) WHO shall not be bound by any obligation of confidentiality or restriction on use to the extent it is clearly able to demonstrate that any part of the Information:

a) was known to WHO prior to any disclosure by the Company to WHO; or
b) was in the public domain at the time of disclosure by the Company to WHO; or
c) becomes part of the public domain through no fault of WHO; or
d) becomes available to WHO from a third party not in breach of any legal obligations of confidentiality to the Company.

(4) The Company undertakes to abide by similar obligations of confidentiality and restrictions on use as contained in paragraphs 2 and 3 above with regard to the Testing Results (regardless of whether or not such Testing Results have been marked as "confidential").

(5) The provision of Product(s), Information, and Testing Results shall not in itself be construed as conveying rights under any patents or other intellectual property which either Party may have or may hereafter obtain.

(6) Subject to the protection of each Party’s confidential information and the provisions of this paragraph 6, Testing Results may be published by either Party. In order to avoid prejudicing confidential information of the other Party, the submitting Party will transmit to the other Party for its review, the material intended to be published at least 30 (thirty) working days before a proposed publication is submitted to any editor, publisher, referee or meeting organizer. In the
absence of an objection by the other Party within the 60-day period concerning prejudice to its confidential information, and provided that all other conditions of this paragraph 6 have been met, the publication may proceed.

In connection with the foregoing, it is understood and agreed that notwithstanding any other provisions in this Agreement, WHO shall be entitled to evaluate and publish the Testing Results, and to exclusively control this evaluation and the content of the aforesaid publication, provided that in order to avoid prejudice to the Company’s confidential Information disclosed to WHO pursuant to paragraphs 1 and 2 above, WHO shall submit any proposed publication to the Company for review in accordance with the provisions of paragraph 6. For the avoidance of any doubt, the Company shall only be entitled to object to a proposed publication if and to the extent it contains any confidential Information of the Company, and not on the grounds that the Company is not satisfied with the Testing Results and/or does not agree with WHO's evaluation thereof.

The Company shall not proceed to the publication (or any other public disclosure) of any of the Testing Results until such Results have been published by WHO and until the proposed publication has been submitted to WHO for review in accordance with the provisions of paragraph 6.

All publications of the results of any evaluation and testing activities carried out under this Agreement shall include the following statement:

“This investigation was carried out as part of the "WHO Malaria Rapid Diagnostic Test (RDT) Product Testing Programme ".

Other than as provided herein before, neither Party shall, in any statement or material of an advertising or promotional nature, refer to the relationship of the Parties under this Agreement or to the relationship of the other Party to the Product(s). The Company shall not, at any time, use, nor allow any other parties to use, the participation in the Product Testing Programme and/or publication by WHO of the Testing Results for commercial or promotional purposes. Under no circumstances shall the Company or any other party be authorized to refer to WHO, the Company's participation in the Product Testing Programme, and/or the publication of the Testing Results by WHO, in any statement or material of an advertising or promotional nature, press release and/or similar public statement and/or other material aimed at promoting the Company, any other party and/or the Product(s).
(7) The Company shall provide the Information and sufficient quantities of the Product(s) to WHO, or WHO’s designee(s), free of charge. Upon receipt of a written request to that effect, the Company shall furthermore pay any and all costs relating to the evaluation and testing process hereunder to WHO, or WHO’s designee(s), in advance, in accordance with WHO’s instructions. In the event that WHO, or its designee(s), do not receive the Information, and sufficient quantities of the Product(s) by the required deadlines, WHO shall be under no obligation to arrange for the performance of any evaluation or testing activities in relation to the Product(s). Any balance of funds provided by the Company, and remaining unspent upon the conclusion of the testing and evaluation process shall be returned to the Company, unless otherwise agreed by the Parties.

(8) The Company hereby furthermore confirms that it has taken good note of, agrees with, accepts and to the extent applicable, shall abide by, the provisions contained in the document, entitled "Information for Manufacturers on WHO Malaria Rapid Diagnostic Test (RDT) Product Testing Programme."

(9) Any dispute relating to the interpretation or application of this Agreement shall, unless amicably settled, be subject to conciliation. In the event of failure of the latter, the dispute shall be settled by arbitration. The arbitration shall be conducted in accordance with the modalities to be agreed upon by the Parties or, in the absence of agreement, with the rules of arbitration of the International Chamber of Commerce. The Parties shall accept the arbitral award as final.

On behalf of WHO:                          On behalf of the Company:

Signature:                                Signature:
Name:                                     Name:
Title:                                    Title:
Date:                                     Date:
**FORM 3**

**FINAL PRODUCT LIST**

**Note:** Please list up to (number to be specified later by WHO-FIND) products, from the list of Expression of Interest (EOI) already submitted to WHO.

*(Please note that details of products in this form should have previously been submitted to WHO (Form 1), and that no new product submitted in this form can be accepted for this round of testing.)*

<table>
<thead>
<tr>
<th>Manufacturer Name</th>
<th>Product 1</th>
<th>Product 2</th>
<th>Product 3</th>
<th>Product 4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Product name&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Catalogue No</td>
<td>Product name&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Catalogue No</td>
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<td></td>
<td></td>
<td>Product name&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Catalogue No</td>
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<td>Product name&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Catalogue No</td>
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<td></td>
<td></td>
<td></td>
<td>Product name&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Catalogue No</td>
</tr>
</tbody>
</table>

<sup>1</sup> Write precise name as it should appear in WHO publications, include ™ ® etc.

Name: ____________________________  Signature: ____________________________

Designation / position: ____________________________  Date: ____________________________
FORM 3

Submit this form by email and hard copy to:

Izabela Suder-Dayao
WHO/TDR
20 Appia Avenue
1211 Geneva
Switzerland
Tel: +41 (22) 791 2261
Fax: +41 (22) 7914854

E-mail: suderi@who.int and Malaria_rdt@who.int

Not later than: 2 November 2012
JOINT-SUBMISSION AND JOINT-LISTING OF PRODUCTS

In cases where products with different names are produced on the same production line, a single product may be submitted for testing and identical products may be jointly listed with the results. The manufacturer of the each separate product should submit a completed EOI. (Such co-submission will require a written application from all the companies concerned and provision of evidence that the products are the same (in the form of a letter signed by the entity indicated as manufacturer (assembler), and a letter signed by the entity or entities indicated as owner(s) of the other products listed as identical). (Please fill the Table on the next page).

In this context, 'manufacture' or 'assembly' indicates production of the test to a state in which it is contained in packaging designed to protect it from environmental degradation (i.e. moisture-proof envelope), including conduct of the quality assurance process in place to ensure product quality. The name of the company which is the operator of the site of manufacture or assembly will be indicated in the list of jointly listed products, together with the name of the company or companies owning the identical products.

In the case of jointly listed products, if one product included in a list of jointly listed products is deemed by WHO to warrant de-listing due to poor performance on lot testing, all jointly listed products will be de-listed and require re-application for product testing. Where products are submitted individually for testing, they will be deemed to be independently manufactured and removal from the product list will involve only the product(s) named.3

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3 In cases where a product is de-listed due to poor performance, WHO-FIND may require specific lot testing of other products believed to be the same as the de-listed product.
**FORM 4**

**REQUEST FOR JOINT-SUBMISSION AND JOINT-LISTING OF PRODUCTS AS PART OF THE WHO MALARIA DIAGNOSTICS PRODUCT TESTING PROGRAMME**

The following products are manufactured under identical conditions at the same manufacturing site, and are considered re-labelled versions of the same product. It is requested that they be listed as such in the publication of the performance results of product testing by WHO.

It is understood that in the event WHO requires a product to be re-tested due to concerns regarding performance, jointly listed products will be considered as identical and will all be removed from the relevant WHO website lists.

**Details of product submitted for testing and manufacturer of submitted product.**

<table>
<thead>
<tr>
<th>Name of manufacturer of product submitted for testing</th>
<th>Product Name</th>
<th>Catalogue Number</th>
<th>Plasmodium species targeted$^1$</th>
<th>Target Antigen (s)</th>
<th>Format$^2$</th>
<th>Dipstick: D</th>
<th>Cassette: Ca</th>
<th>Card: Cd</th>
<th>Contact person and designation</th>
<th>Address</th>
<th>Email URL</th>
<th>Contact numbers</th>
</tr>
</thead>
<tbody>
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</tbody>
</table>

**Details of product to be listed as identical (re-labelled)**

<table>
<thead>
<tr>
<th>Name of owner / user of re-labelled product name</th>
<th>Product Name</th>
<th>Catalogue Number</th>
<th>Contact person and designation</th>
<th>Address</th>
<th>Email URL</th>
<th>Contact numbers</th>
</tr>
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</tbody>
</table>

**Owner of the Product**

Signature_______________________ Name _____________________________ Designation / position _________________________

**Manufacturer of the Product**

Signature_______________________ Name _____________________________ Designation / position _________________________
NOTE:

A separate signed letter must be provided by the manufacturer submitting product for testing, and the manufacturer/owner of the re-labelled product. Manufacturer requesting for joint submission of a product should send the Expression of Interest (Form 1) and Form 4 by 24 September, 2012.
To all manufacturers

In reply please refer to:

Your reference:

9 October 2012

Dear Manufacturer,

This letter is to acknowledge acceptance of your Expression of Interest in the WHO Malaria RDT Product Testing Programme: Round 5

The letter contains important reminders and information regarding the following topics.

1. Limits on number of products for submission
2. Required documents and future deadlines
3. Special notes on ISO requirements
4. Availability of panels of cultured parasites for preliminary testing of products by manufacturers: ‘manufacturer’s panel’
5. Summary of product testing procedure
6. Provisional timeline for product testing
7. Relationship of product testing to WHO RDT procurement of malaria RDTs

Please do not hesitate to contact me with any questions or concerns.

Yours sincerely,

Jane Cunningham
Technical Officer
WHO/HTM/GMP
Round 5 of WHO Malaria RDT Product Testing Programme

1. **Limit on number of products to be submitted by each manufacturer**

Due to the high volume of response to the EOI and to ensure comparability of results across Rounds, the number of products from each company will be limited to ONE (1) in Round 5. The only exception is for manufacturers with products listed in Annex 3 (requirements for resubmission), these will not count against the final limit of one product per manufacturer, and should be submitted in addition to the one optional products, if the manufacturer wishes them to be eligible to remain on the WHO malaria RDT procurement list.

2. **Required documents and deadlines**

**By 2 November 2012:** the following items (A-E) are required to qualify for participation in Round 5 of the WHO Product Testing Programme.

Kindly refer to the Annexes and Forms of the accompanying document: EOI-Annex 1_2_3_Round 5_version 2.

All documents must be submitted by E-mail by 2 November 2012, followed by hard copy to:

Izabela Suder-Dayao  
WHO/TDR  
20 Appia Avenue  
1211 Geneva  
Switzerland  
Tel: +41 (22) 7912261  
Fax: +41 (22) 7914854

E-mail: suderi@who.int  
With a copy (c.c.) to Malaria_rdt@who.int

**A. TWO original signed copies of the Confidentiality Agreement** (Form 2). One original will be signed by the Director of the Global Malaria Programme (GMP) and returned to you by mail.

**B. Valid ISO 13485:2003 certificate for ALL sites manufacturing and packaging the product(s) (minimum expiry date 14 January 2013).**

   a. Special conditions may apply as detailed below.

      i. In cases where an audit has been undertaken by an ISO 13485:2003 auditor, but the certification is not yet available, WHO will accept a signed letter from the auditor confirming that an audit has been undertaken and the certificate is in process. The certificate must be submitted no later than the deadline for final submission of products (14 January 2013).

---

1 These documents were sent with the original announcement of the Round 5: EOI and are reattached to this correspondence - File name: Microsoft Word - EOI-Annex 1_2_3_Round 5_version 2. Alternatively, they can be downloaded at http://www2.wpro.who.int/sites/rdt/who_rdt_evaluation/call_for_testing_round5.htm

2 It is necessary for manufacturers to maintain current ISO13485:2003 certification for all manufacturing sites of a given product for this product to remain eligible for the WHO procurement list. Should additional sites be added after the product testing results are released, certificates for these sites must be submitted to WHO prior to release of products. WHO may de-list products found not to have complied with this requirement.
ii. A product maybe accepted into the Product Testing Programme if the following three conditions are met:

1. A current ISO13485:2003 is submitted covering all site(s) of manufacturing and packaging of the product;

2. A signed letter from the holder/company of the ISO13485:2003 stating that all manufacturing and packaging of the named products takes place under the facility covered by the ISO certification(s).

3. The submitting company must obtain ISO9001 by March 2014 for the products to remain on the list of products tested under the WHO Product Testing Programme and in subsequent publication of results.

C. **Provision of acceptable heat stability protocol(s)** undertaken as part of internal quality assurance (information in ANNEX 4).

D. **Final Product List** (Form 3). Maximum oneproduct, in addition to products qualifying for compulsory resubmission (Annex 3) can be listed. These cannot be changed or replaced at a later date. Please ensure product name and product code are correct.

E. **Product leaflets.** Please ensure that product leaflets sent by email, hard copy and accompanying the RDT shipment are accurate and identical. In the case of any discrepancies, the leaflets/instructions accompanying the RDT shipment will apply.

3. **Ordering panels of cultured parasites (P. falciparum) for preliminary testing of products by manufacturers (optional)**

A panel of samples derived from cultured *P. falciparum*, diluted and preserved at -80°C, is available, free of charge, but the receiver must cover all shipping charges (see below). This panel will be a subset of the Phase One panel used for product testing, and is intended to allow manufacturers to assess product quality prior to submitting lots to the Product Testing Programme.

The panel is detailed in Table 1 and can be **requested by completing and returning the ‘Order Form’ on page 7**. Accessing this panel is optional, but recommended. Shipments are ready for release immediately.

This 'manufacturer's panel' has been prepared at US CDC and consists of aliquots of 5 cultured *P. falciparum* parasite lines from geographically different endemic areas. Each of these samples is provided at two parasite dilutions: 200, and 2,000 parasites per µl. The panel has been tested against a number of commercially-available HRP2-detecting and pLDH-detecting RDTs. The results indicate that all 2000 parasites/microL concentrations are expected to be detected by good quality RDTs. The 200 parasites/microL samples can be detected by some HRP2-detecting and pLDH-detecting RDTs but these samples are close to the detection limit of currently-available tests. Should your products fail to detect samples at 2000 parasite/microL, it is therefore likely that these products will not perform well in terms of antigen detection against the complete product testing panel, and your company should seriously consider whether or not you submit these products for further evaluation. As stated previously all results of RDTs submitted to WHO for evaluation will be published.
Table 1: Sample panel available to manufacturers for screening prior to product submission.

<table>
<thead>
<tr>
<th>Sample type</th>
<th>n</th>
<th>Antigen type and concentration</th>
<th>Origin</th>
<th>Testing conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>MANUFACTURERS PANEL</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P. falciparum (Pf) culture lines</td>
<td>5</td>
<td></td>
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</tr>
<tr>
<td>ID: Name of the Pf strains:</td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>ID: US03F Benin I/Benin I</td>
<td>A</td>
<td>10.18 4.23 0.71</td>
<td>Benin, West Africa</td>
<td>Dilutions prepared: 200 and 2000 or 5000 parasites/µL</td>
</tr>
<tr>
<td>ID: US04F Nigeria XII/Nigeria XII</td>
<td>B</td>
<td>5.93 4.69 0.63</td>
<td>Nigeria, West Africa</td>
<td></td>
</tr>
<tr>
<td>ID: US03F FC27 A3/FC27-A3</td>
<td>B</td>
<td>19.5 7.9 1.21</td>
<td>Papua, New Guinea</td>
<td></td>
</tr>
<tr>
<td>ID: US03F PH1/PH-1</td>
<td>C</td>
<td>5.9 2.54 0.96</td>
<td>Philippines</td>
<td></td>
</tr>
</tbody>
</table>

Note: samples characterized by microscopy, molecular species diagnosis, Pf HRP2 sequencing, and quantitative antigen ELISA.

* Indication of the parasite antigen (Pf HRP2 types A / B / C and HRP2, pLDH and aldolase antigen content (ng/mL) at 200 parasites/µL).

Geographical origin of parasite strains

* Pf culture line used as the reference standard for RDT stability testing at the CDC and by the manufacturers participating in the WHO Product Testing Programme.

n = number of samples, p/µL = parasites per microlitre of blood.

Each requesting manufacturer will receive a labeled panel consisting of frozen samples of each of these culture lines, as 15 aliquots of 50 microL diluted to 200 parasites/microL and 2000 parasites/microL (Total 15 x 2 x 5 = 450 aliquots). Panels are provided free of charge, but the manufacturer is responsible for organizing and paying the costs of a courier, and organizing permits and all passage through ports and customs once the sample has left the production site at the United States Centre for Disease Control and Prevention (US CDC) in Atlanta, USA. Note the samples should be shipped on dry ice (-78°C).

The courier company handling the shipment needs to liaise with the Mr Jeffrey Glenn; email khi2@cdc.gov for arranging the schedules of pick up of the panel. Loss or damage to the shipments is the responsibility of consignee, and the shipper engaged by the consignee. Due to the limited number of available samples, WHO can not guarantee that damaged or lost shipments will be replaced.

4. Summary of product testing procedure (Figures 1a,b)

Figures 1 and 2 give a brief outline of product testing. A detailed description of the Product Testing Programme and Standard operating procedures (Methods Manual for Product Testing of Malaria Rapid Diagnostic Tests (Version 5) can be found at the following website: http://www.wpro.who.int/sites/rdt/documents/list.htm
Figure 1:

a) Outline of the Product Testing Protocol

b) Phase 1 and Phase 2: Challenge Panel for Malaria RDT Product Testing

<table>
<thead>
<tr>
<th>Panel</th>
<th>Panel samples</th>
<th>RDTs tested at each dilution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase 1</td>
<td>Pf culture panel</td>
<td>20 lines</td>
</tr>
<tr>
<td>Phase 2</td>
<td>Wild type <em>P. falciparum</em></td>
<td>≈100</td>
</tr>
<tr>
<td></td>
<td>Wildtype <em>P. vivax</em></td>
<td>≈40</td>
</tr>
<tr>
<td></td>
<td>Negative panel</td>
<td>100</td>
</tr>
</tbody>
</table>

Note: The final panel may vary slightly according to the availability of samples acceptable for testing after characterization is completed.

Note: Each lot **must detect** ≥ 80% of the high density culture samples in **Phase 1** before progressing to Phase II evaluation panel.
5. **Provisional timetable for product testing (times may change)**

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<tbody>
<tr>
<td>Panel available to manufacture (OPTIONAL)</td>
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<td>Product arrival at US CDC</td>
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<td>Round 5 WHO Product Testing begins</td>
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<tr>
<td>Completed product testing</td>
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<tr>
<td>Results sent to manufacturers and reviewed x 30 days</td>
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6. **Relationship of product testing to WHO RDT procurement**

As with the previous rounds of WHO Product Testing, the results of the Round 5 will be added to prior Rounds and form the basis of WHO procurement recommendations and the WHO tendering programme. Results from subsequent Rounds replace results obtained for the same product in previous Rounds. At present, these recommendations are specific to a product catalogue code, manufactured by one or more manufacturing facilities with proof of valid ISO 13485:2003 certificate(s).

The results of WHO Malaria RDT Product Testing also currently form the basis of the WHO Prequalification of Diagnostics Programme ‘laboratory evaluation’ component for malaria RDTs. For a full description of procedures and requirements of the WHO Prequalification of Diagnostics Programme can be found here:

http://www.who.int/diagnostics_laboratory/evaluations/en
Order Form - 'Manufacturers Panel' - culture-derived P. falciparum samples

<table>
<thead>
<tr>
<th>Manufacturer Name</th>
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<tbody>
<tr>
<td>Manufacturer (consignee) address and email</td>
<td></td>
</tr>
</tbody>
</table>

| Courier company contracted for transport (including full contact details). |  |

Note: It is entirely the manufacturer's responsibility to contract the shipping agent (courier) and undertake all necessary payments for transport, including supply of packaging materials and dry ice. The manufacturer should be experienced at transporting goods on dry ice (-78°C). Note that the consignment contains dead malaria parasites in human blood:

**Category B Biological Substance - UN 3373**
- Human Blood Samples (Frozen) containing dead malaria parasites
- Quantity: 150 vials containing 50 µL
- For Laboratory Testing Only
- Human material containing no animal material and not of tissue culture origin.

The shipping agent (courier) MUST contact CDC (see details below) beforehand to arrange pick-up of samples. US CDC has the discretion to vary the preferred pick-up date.

Contact details for ordering panels:

<table>
<thead>
<tr>
<th>Order by email:</th>
<th>Jeff Glenn : <a href="mailto:khi2@cdc.gov">khi2@cdc.gov</a></th>
<th>cc: <a href="mailto:vom9@cdc.gov">vom9@cdc.gov</a>; <a href="mailto:Malaria_rdt@who.int">Malaria_rdt@who.int</a></th>
</tr>
</thead>
</table>

Contact details for courier:

| Consigner address for courier | Jeffrey Glenn  
Malaria Branch, Division of Parasitic Diseases and Malaria  
Centers for Disease Control & Prevention  
Bldg. 23, Room 10-169 Mailstop D-67  
1600 Clifton Road  
Atlanta, GA 30329 USA  
ph: 404.718.4427  
Email: khi2@cdc.gov |

GENERAL INFORMATION ON PROGRAMME AND TIMELINES : ROUND 5

This document includes details of Round 5 of World Health Organization (WHO) Malaria Rapid Diagnostic Test (RDT) Product Testing and criteria for inclusion of products. The Malaria RDT Product Testing Programme is a collaboration of the WHO Global Malaria Programme (GMP), the Foundation for Innovative New Diagnostics (FIND) and the US Centers for Disease Control and Prevention (CDC).

The only action necessary now for a manufacturer interested in participating in Round 5 WHO Product Testing is to send the details of all products considered for submission in accordance with the instructions described below. Such an Expression of Interest will not be binding on either party, but must be received electronically by WHO by 24 September 2012 to enable submission of the listed products in the fifth round of testing (which is scheduled to commence at the end of January of 2013).

A. Introduction

WHO is proposing to undertake another round of evaluations to assess the performance of antigen-detecting malaria rapid diagnostic tests (RDT). All product testing will be conducted at the Malaria Branch, Division of Parasitic Diseases, and Centers for Disease Control and Prevention, Atlanta, U.S.A., in collaboration with the Foundation for Innovative New Diagnostics (FIND), with an optional stability assessment performed at the site of manufacture.

1. A total of 2200 Malaria RDTs, consisting of 1100 tests and standard kit contents, from each of two separate lots of each product, will be required to be submitted to the Programme. Testing will be conducted in two phases. Phase 1 of the testing process will be performed against a panel of cryo-preserved preparations of cultured *P. falciparum* parasites and 20 clean-negative samples. Phase 2 will be performed against a panel containing diluted cryo-preserved preparations of wild parasites (*P. falciparum* and *P. vivax*), and parasite-negative samples. Products that have previously achieved the WHO procurement criteria will not be required to be tested in Phase 1 of the product testing programme. Manufacturers are responsible for the RDT and courier costs and any other associated costs of transport of RDTs to US CDC.

2. Manufacturers have the option to obtain a subset of the product testing panel prepared from cultured *P. falciparum* malaria parasites for their own quality control testing prior to submission of products to the WHO Product Testing Programme, and for stability testing at the manufacturing site. There is no charge for this panel but manufacturers are responsible for the courier costs (from CDC to the manufacturing site) and any associated costs of transport and importation.

3. The opportunity for submissions of request for inclusion of products (Expression of Interest, EOI) in Round 5 of WHO Product Testing will close on 24 September 2012. Only products listed on the Form 1 of the submission will be eligible for Round 5. WHO reserves the right to later limit the number of products per manufacturer if the total number of products in the EOI is beyond the capacity for testing by the Programme in a single round of Product Testing. In past rounds, this number has been restricted to 2 or 3 products.

4. The WHO Malaria RDT Product Testing Programme will publish the list of products and associated performance data in various formats including: i) a dedicated WHO website page ii) electronic and hard copy of Round 5 results iii) electronic and hard copy of compiled Rounds 1-5 results. In advance of all publications, manufacturers will be informed of the performance results, in accordance with the terms of the attached sample Confidentiality Agreement. (The Confidentiality Agreement in Form 2 should not be signed at this stage, but will be required at the time of final product submission for the WHO Malaria RDT Product Testing Programme – see diagram on page 6).
5. As with previous WHO Product Testing rounds, results of Round 5 will form the basis of procurement recommendations of WHO and the WHO tendering programme and will guide future procurement of RDTs by WHO, other UN Agencies and national health authorities. Publication of data on product performance and/or inclusion in the above mentioned website list does not guarantee that the RDTs in question will actually be procured by WHO or any other party.

6. In order for a product to be published in the ‘Summary Results of Rounds 1-5’ document and published on the WHO and FIND websites, and to be eligible for WHO procurement, manufacturers are now required to resubmit within less than 5 years. Therefore, any manufacturer who submitted products to Round 1 (2008), who has not already resubmitted products to future rounds (Rounds 2,3,4), and wants to continue to be listed in the Product Testing Report and be eligible for WHO procurement, must participate in Round 5. A list of manufacturers and products affected by this policy is included in Annex 3.

Voluntary resubmission of products (from Rounds 2,3,4) is still acceptable and as in previous years, the results of earlier rounds will be replaced in the performance report by results of subsequent rounds to which the product is submitted.

7. The manufacturer of a listed product for which the product specifications, as outlined in Annex 2, have been changed, is requested to inform WHO of such changes prior to the commercial release of the changed product. WHO may remove a product from the website list or require re-submission of a product for performance testing if changes in product specifications indicate that the RDT should be considered a new product, or performance data obtained from WHO-FIND lot testing services in the field are considered to be consistently outside those of the product testing programme published by WHO.

8. The list of submitted products does not in any way imply an endorsement, certification, warranty of fitness or recommendation by WHO of any company or product for any purpose, and does not imply preference over products of a similar nature that are not mentioned. WHO furthermore does not warrant that: (1) the list is complete and/or error free; and/or that (2) the products listed are of acceptable quality, have obtained regulatory approval in any country, or that their use is otherwise in accordance with the national laws and regulations of any country, including but not limited to patent laws. Inclusion in the list does not furthermore imply any approval by WHO of the products in question (which is the sole prerogative of national authorities).

9. Participation in WHO Malaria RDT Product Testing and publication by WHO of the testing results may not be used by the manufacturers and suppliers concerned for commercial or promotional purposes. With respect to the manufacturers' or suppliers' participation in the Product Testing Programme, under no circumstances is a manufacturer or supplier authorized to refer to WHO and/or FIND, the publication of the testing results by WHO and/or FIND and/or inclusion in the website list, in any statement or material of an advertising or promotional nature, press release and/or similar public statement and/or other material aimed at promoting the manufacturer or supplier and/or its products.

B. Criteria for entry to the WHO Malaria RDT Product Testing Programme and Timelines

Conditions of entry are derived from the recommendations of WHO expert consultations at Geneva, Kisumu and Atlanta in 2006, and confirmation in subsequent consultations of the WHO-FIND Malaria RDT Evaluation Programme Steering Committee (formerly referred to as the Malaria RDT Specimen Bank Review Committee). Conditions for testing of products as part of the WHO Malaria RDT Product Testing Programme¹ (see Diagram on page 6)

¹ It is planned to include a product specific audit as a criteria in the future, through a mechanism to be determined by WHO.
1. **By 24 September 2012:** Submission of an Expression of Interest (EOI) to WHO (as in the attached Form 1).

   Documents to be submitted by E-mail (scanned copies) and hard copy to:

   Izabela Suder-Dayao  
   WHO/TDR  
   20 Appia Avenue  
   1211 Geneva  
   Switzerland  
   Tel: +41 (22) 791 2261  
   Fax: +41 (22) 791 4854  
   E-mail: suderi@who.int  
   With a copy to Malaria_rdt@who.int

2. **By 2 November 2012 (if EOI is accepted) all items listed below must be received by e-mail as scanned copies. Hard copies must follow by courier.** Fulfillments of the requirements for taking part in Round 5 of WHO Product Testing includes:

   *NB: Do not send the below documents before notification by WHO of acceptance of products listed in Form 1.*

   a) Valid ISO 13485:2003 from all sites where the product(s) is manufactured

   b) Provision of an acceptable heat stability protocol of internal quality assurance (ANNEX 4).

   c) Submission of 2 original signed copies of the Confidentiality Agreement (Form 2) and acceptance of conditions for product testing and publication of results.

   d) Final Product List (Form 3)

   e) Product leaflets/package insert

   **Please ensure that product leaflets sent by email, hard copy and accompanying the RDT shipment are accurate and identical. In the case of any discrepancies, the leaflets/instructions accompanying the RDT shipment will apply.**

3. **By close of business (COB) 14 January 2013:** Delivery of Malaria RDTs to US CDC, Atlanta. (see point E below) at manufacturer’s cost

4. **Re-labeled products that are manufactured at the same site and under the same conditions as a tested product, and fulfill the criteria in Form 4, may be jointly listed with the tested product under the criteria and conditions listed in Form 4.**

   The above actions should be undertaken if and when WHO or FIND so notifies the manufacturer. No product testing will take place unless the manufacturer has fulfilled the above conditions by the dates set by WHO and FIND and in accordance with WHO and FIND’s instructions.
ANNEX I

C. Supply of products for testing

- A total of 2200 tests consisting of 1100 tests, and standard contents, from each of the two separate lots must be submitted to the US CDC, Atlanta, according to instructions provided by WHO and/or FIND.

- All RDTs must be received at US CDC by COB 14 January 2013 in order to be accepted for product testing. (Temperature monitors for the duration of the transportation can be obtained from WHO free of charge at request)

- All products will be stored in an air conditioned, temperature monitored room from the time of receipt until the actual testing occurs (the product testing site will determine the order in which testing will be conducted)

- If a product does not display sufficient performance against the Phase 1 panel, the lot will not be tested against the Phase 2 panel. Sufficient performance is defined as ≥ 80% panel detection score against 2000 parasites/μl samples, with ≤ 25% false positive rate against 20 clean-negative samples.

**Important note on RDT format**

Manufacturers may submit commercially-available antigen-detecting lateral flow products in any format and for any target antigen. RDTs with the same product name but different format (e.g. cassette and dipstick) are considered as separate products and will require separate submission and testing. Results are interpreted through visual reading. On publication of the testing results, the introductory text accompanying the table of product performance characteristics will emphasize the current WHO recommendation that cassettes are preferred to dipsticks for field use in endemic countries. Manufacturers are therefore advised to consider submitting only tests in cassette format.

It is noted that previous Rounds of WHO Malaria RDT Product Testing have evaluated few products targeting *P. falciparum*-specific pLDH. These products may have advantages in certain endemic settings and therefore, we encourage manufacturers to seriously consider submission of such products.

D. Oversight:

The WHO Malaria Specimen Bank (currently at US CDC), is the repository of characterized samples against which product testing will occur, and includes culture-derived and wild-type malaria parasites, and parasite negative samples. The wild-type parasites are collected from a geographically-diverse network of collection sites in Asia, Africa and South America, and prepared according to standard protocols.²

The WHO-FIND Malaria RDT Evaluation Programme Steering Committee (formerly referred to as the Malaria RDT Specimen Bank Review Committee) oversees the technical and logistical aspects of the testing and evaluation process, including the development of Standard Operating Procedures (SOPs), oversight of ethical approval for the collection sites contributing to the Specimen Bank (including submission to the WHO Ethics Committee, and local ethical review board) and oversight of the product testing and reporting of results.

Terms of Reference of the WHO-FIND Malaria RDT Evaluation Programme Steering Committee

The WHO-FIND Malaria RDT Evaluation Programme Steering Committee (formerly referred to as the Malaria RDT Specimen Bank Review Committee) will provide recommendations to WHO and FIND on:

- Development and modifications of SOPs for specimen collection and use
- Collection, characterization and maintenance of the Specimen Bank
- Policy on access to the Specimen Bank
- Protocols for laboratory-based testing of the accuracy and stability of malaria RDTs, including product testing and lot testing
- Review and interpretation of the results of product testing, prior to publication.

Composition

Core:

WHO/GMP [2] (as of 1 July 2012)
Foundation for Innovative New Diagnostics (FIND) [2]
US Centers for Disease Control and Prevention (CDC) [2]
Médecins sans Frontières [1]
Collection sites: 1 African [1]
1 non-African [1]
Specimen characterization centers:
- Hospital for Tropical Disease, UK [1]
- Army Malaria Institute, AU [1]
WHO Malaria RDT Product Testing Programme

Step 1: Submission of Expression of Interest (Form 1 +/- Form 4)
Deadline for Receipt 24 September 2012

Step 2: WHO-FIND sends EOI Acceptance letter to manufacturers, final number of tests per manufacturers that can be submitted to Round 4 and instructions for obtaining the optional culture panel from CDC for manufacturer quality control testing.
5 October 2012

Step 3:
- i) Submission of ISO 13485:2003 from ALL manufacturing sites and provision of heat stability protocol of internal quality assurance (see Annex 4)
- ii) TWO signed ORIGINAL copies of Confidentiality Agreements (Form 2)
- iii) Final list of products (Form 3 )
- iv) Corresponding product inserts/leaflets for each product submitted.
- v) OPTIONAL - Request for temperature monitor for duration of RDT transport
Deadline for Receipt 2 November 2012

Step 4: Review of the submissions by Steering committee
November 2012

Step 5: WHO sends Confirmation of Acceptance of Final list of products for the Product Testing Programme
8 November 2012

Step 6: Applicant submits a total of 2200 tests and standard kit contents consisting of 1100 tests from each of two separate lots to US CDC
Deadline for Receipt 14 January 2013

Step 7: Applicants optionally request and obtain parasite specimen samples from US CDC for the stability testing at manufacturer site
February 2013

Step 8: Applicant optionally submits results of the stability test performed at the manufacturer site every 3 monthly until the end of the specified shelf life.

Step 9: Manufacturers reports with product specific results released to applicants.
Feb-March 2014

Step 9: WHO-FIND Publication of Round 5 and compiled Rounds 1-5 Product Testing Results
April-May 2014
E. Further Information

Further information on the Product Testing Programme can be found in:


All the above documents can be found at: [http://www.wpro.who.int/sites/rdt/documents/list.htm](http://www.wpro.who.int/sites/rdt/documents/list.htm); [www.finddiagnostics.org](http://www.finddiagnostics.org) and [www.who.int/tdr](http://www.who.int/tdr) or can be obtained by sending an email to: Malaria_rdt@who.int
DEFINITION OF A 'PRODUCT' AND 'LOT'

It is necessary to clearly define the terms “product” and “lot” to implement the proposed testing scheme, as product testing results should be applied only to a specifically defined and labelled product, and lot testing results should be applied only to a clearly defined and labelled lot.

(1) **Lot.** The definition of a “lot” is the responsibility of the manufacturer. All manufacturers must have current ISO 13485:2003 or US FDA 21 CFR 820 certification and an appropriate “lot” definition must be compatible with this.

(2) **Product.** Defining a malaria RDT “product” for the purposes of a product testing scheme is more difficult. However, this definition should be based on consistency in overall design and on the major constituents of the RDT that are likely to have a significant impact on RDT stability and accuracy. Assuming that evidence of equivalent performance can be provided, the following applies:

   a) Similar but re-labelled products from various manufacturers should generally be considered different products (see joint listing of products below) but may be considered the same product if specifically indicated by the manufacturers concerned.

   b) **Monoclonal antibodies (Mab)** – A change in target epitope, or of the species from which target antigen for Mab development is derived, should constitute a new product. A change in source (manufacturer) or modifying the amount of Mab used in a test would not constitute a new product if the Mab cell line originated from the same source.

   c) **Dye conjugate** (signal reagent) – A change in specification or type of label (e.g. colloidal gold, latex particle or liposome) should constitute a new product, but a change in manufacturer/source should not.

   d) **Format** – A change in assay presentation between, for example, a dipstick, cassette or card, constitutes a new product.

   e) **Buffer** – A change in assay buffer constituents or pH does not constitute a new product.

(3) **Equivalence of performance.** Where changes made have the potential to significantly affect accuracy of the RDT, including changes in raw materials or components, including Mabs, signal reagents, buffers, nitrocellulose membranes, or in cassette design, equivalence of performance data should be provided to WHO to demonstrate that the modified product has a performance equivalent to, or better than, that previously submitted to formal testing. As this is an activity that should be performed as part of routine internal QA by the manufacturer, demonstration and notification of equivalence should not result in additional costs or workload.

**Reference:**

1. Towards Quality Testing of Malaria RDT-Evidence and Methods, 2006, World Health Organization
The following products have not been evaluated within the last 5 years and must resubmitted to Round 5 in order to continue to be listed in the Summary of WHO Malaria RDT Product Testing (Rounds 1-5) and considered for WHO tendering and procurement.

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>Product</th>
<th>Catalogue #</th>
</tr>
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<tbody>
<tr>
<td>Access Bio, Inc.</td>
<td>CareStart Malaria pLDH (PAN)</td>
<td>G0111</td>
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<tr>
<td></td>
<td>CareStart Malaria HRP2/pLDH (Pf/PAN) COMBO</td>
<td>G0131</td>
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<tr>
<td></td>
<td>CareStart Malaria HRP2 (Pf)</td>
<td>G0141</td>
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<tr>
<td>Acon Laboratories, Inc.</td>
<td>Malaria Plasmodium falciparum Rapid Test Device (Whole Blood)</td>
<td>IMA-402</td>
</tr>
<tr>
<td>Amgenix International, Inc.</td>
<td>OnSight - ParaQuick (Pan, Pf) Test</td>
<td>536-25DB</td>
</tr>
<tr>
<td>Biosynex</td>
<td>Immunoquick Malaria Falciparum</td>
<td>0502_K25</td>
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<tr>
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<td>Immunoquick Malaria +4</td>
<td>0506_K25</td>
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<tr>
<td>Diagnostics Automation/Cortez Diagnostics Inc.</td>
<td>Malaria P.F/Vivax</td>
<td>172110P-25</td>
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<tr>
<td>Human GmbH</td>
<td>Hexagon Malaria</td>
<td>58051</td>
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<td>Hexagon Malaria Combi</td>
<td>58024</td>
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<tr>
<td>IND Diagnostic Inc.</td>
<td>One Step Malaria Antigen Strip</td>
<td>820-1</td>
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<tr>
<td>Innovatek Medical Inc.</td>
<td>Quickstick Malaria Antigen Test2</td>
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<tr>
<td>Intec Products, Inc.</td>
<td>ADVANCED QUALITY™ MALARIA (p.f) POCT</td>
<td>ITP11002TC1</td>
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<tr>
<td>Inverness Medical Innovations, Inc.</td>
<td>Binax Now Malaria</td>
<td>IN660050</td>
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<tr>
<td>J. Mitra &amp; Co. Pvt. Ltd</td>
<td>Advantage P.f. Malaria Card</td>
<td>IR016025</td>
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<td>Advantage Pan Malaria Card</td>
<td>IR013025</td>
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<td>Advantage Mal Card</td>
<td>IR221025</td>
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<tr>
<td>Premier Medical Corporation Ltd.</td>
<td>First Response Malaria Ag HRP2</td>
<td>II3FRC30</td>
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<tr>
<td>Span Diagnostics</td>
<td>Parahit-Total Device Rapid Test for <em>P. falciparum</em> and Pan malaria species</td>
<td>25989</td>
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<tr>
<td>Standard Diagnostics</td>
<td>SD Bioline Malaria Ag Pf</td>
<td>05FK50 (02-4)</td>
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<tr>
<td>Unimed International</td>
<td>FirstSign – Malaria Pf Card Test</td>
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<tr>
<td></td>
<td>FirstSign – ParaView-2 (Pv + Pf) Card Test</td>
<td>2102CB-25</td>
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1 Alere companies

2 Co-listed with IND Diagnostics - One Step Malaria Antigen Strip (820-1)
INTERNAL HEAT STABILITY PROTOCOL AT MANUFACTURING SITE

As evidence of stability testing, WHO will accept protocols submitted by manufacturers that comply with the points listed below. However, based on the recommendations of the WHO Malaria Specimen Bank Committee in February 2010 (Bangkok, Thailand), WHO will continue to supply manufacturers participating in WHO Product Testing with cultured parasites but manufacturers are no longer required to submit results of stability testing to WHO.

The following standards for stability testing are modified from Hornback, L.A., originally published in IVD Technology, April 2004 (See references)

A stability study for in-vitro diagnostic device (IVD) reagents has the same elements as those dictated for stability testing of drugs including the following:

- A written stability testing programme designed to assess the stability characteristics of IVDs.
- A stability protocol with predefined acceptance criteria that can be correlated to the label claims.
- Testing multiple unique product lots. A stability study is required to use three product lots that are manufactured when the manufacturing process has been well defined and can be consistently executed.
- Evaluation of each stability attribute via a statistically valid sample size and testing intervals. The sample size should be sufficient to overcome the precision of the test method used, considering the cumulative effect of all elements of the test system (i.e., individual reagents and instruments). The test intervals should be chosen so that trends may be discerned from variability of the data. At a minimum, stability testing should continue to one time interval past labeled expiration.
- Control of material storage. For real-time stability testing, the IVD reagents should be stored under the conditions stated on the label (e.g., temperature, humidity, light protection).
- Testing IVD in the same container-closure system as the marketed product.
- Use of reliable, meaningful and specific test methods.

The requirement set forth in the last bullet point implies the use of blood samples containing adequate parasite antigen to produce a clear test line on the RDT near the minimum equivalent parasite density that the RDT is expected to detect.

Use of Accelerated Study Data

Accelerated stability studies are useful for predicting the shelf life of IVD. Such accelerated studies subject IVD to extreme conditions—typically elevated temperatures—to the extent that the device endures significant and measurable deterioration during the testing period. Mathematical extrapolations, such as the Arrhenius equation, are then used to calculate the predicted shelf life of the IVD. However, not all IVD follow a predictable degradation rate. Some products will perform acceptably until they fail, in which case only real-time testing will suffice.

According to the United States Food and Drug Administration's Office of In Vitro Diagnostic Device Evaluation and Safety, accelerated stability studies are acceptable in the following situations:

- establishing preliminary claims in new products only if there is sufficient correlation to an existing product and,
- supporting implementation of a change to an existing product.
The European standard EN 13640:2000 provides guidance on not only conducting real-time and accelerated stability studies but also making calculations using the Arrhenius equation. Only real-time stability data are acceptable for testing of either newly licensed IVD or major changes to existing IVD.

References

<table>
<thead>
<tr>
<th>Company name</th>
<th>Product Name¹</th>
<th>Catalogue Number</th>
<th>Plasmodium species targeted²</th>
<th>Target antigen(s)</th>
<th>Format³</th>
<th>Packaging (Individual or bulk)</th>
<th>Number of tests per box</th>
<th>All materials can be included? (lancets, swabs, wells if required)</th>
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FORM 1

<table>
<thead>
<tr>
<th>Product name</th>
<th>Shelf life</th>
<th>Storage temperature recommended by manufacturer</th>
<th>Temperature stability data on which shelf-life is based ('Accelerated' or 'Real time')</th>
<th>Contact person (If appropriate)</th>
<th>Address (for procuring tests)</th>
<th>Email URL</th>
<th>Contact numbers</th>
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</table>

1. Write precisely how it should appear in all WHO publications, include ™ or ®, etc
3. 'Dipstick' refers to simple nitrocellulose strip which requires placement in well. Cassette / card indicates strip enclosed in (plastic) cassette of card.

Signature_______________________   Name _____________________________   Designation / position _________________________

NOTES:

- Please note that the information submitted on this form should be accurate for WHO publication purposes
- This Expression of Interest should be submitted to Izabela Suder-Dayao, WHO/TDR 20 Appia Avenue, Geneva 1211 Switzerland. Email:suderi@who.int, with an e-copy to: Malaria_rdt@who.int, by **24 September 2012**.
Manufacturers should ensure that receipt is acknowledged. The provision of the required product details in this table, and the provision of evidence demonstrating compliance with the requirements set forth in Annex 1, is necessary in order for the products to be considered by WHO for inclusion in Round 5 of WHO Malaria RDT Product Testing.

Only products listed above maybe included in the list of products finally submitted to the Product Testing Programme. WHO reserves the right to limit the maximum number of products that can be submitted by manufacturers, if the listed products in the EOI is beyond the capacity for testing by the Programme in a single round of Product Testing. Manufacturer will be notified accordingly.

If co-listing any product, Form 4 must also be completed and submitted with the EOI.

WHO-FIND will notify a manufacturer if products have been accepted for this round of Product Testing Programme by 24 September, 2012.

The submission of an EOI and/or the aforesaid evidence will neither obligate WHO to accept, nor obligate the manufacturer to actually provide, the listed products for product testing.

**CHECKLIST for manufacturer before Submission of EOI**

1. Completed and signed product specifics (Form 1) – 24 September 2012
2. Completed and signed Co-listing details (if relevant) (Form 4) - 24 Sept. 2012
(signed by both the manufacturer and the owner of the product)
WHO STANDARD CONFIDENTIALITY AND MATERIAL TRANSFER AGREEMENT

Between

.........................................................having its principal offices at .........................................................

.........................................................(hereinafter referred to as "the Company");

and

The World Health Organization, Avenue Appia, 1211 Geneva 27, Switzerland, (hereinafter referred to as “WHO”).

The Company has developed (a) rapid malaria diagnostic test(s), known under the trademark :

......................................................... which test(s) is/are further described in Exhibit 1 attached hereto, (hereinafter referred to as “the Product(s)”, and information relating thereto (hereinafter referred as the “the Information”). WHO is interested in having the Product(s) evaluated and tested in the WHO-FIND Malaria Rapid Diagnostic Test (RDT) Product Testing Programme, jointly coordinated by the WHO and the Foundation for Innovative New Diagnostics (FIND) hereinafter referred to as "WHO Malaria Rapid Diagnostic Test (RDT) Product Testing Programme".

Therefore, the Parties have agreed as follows:

(1) The Company shall disclose and furnish to WHO the Information and sufficient quantities of the Product(s) in order to enable WHO to assess the Information and arrange for such evaluations of the Product(s), as WHO may determine, are reasonably necessary to assess the performance of the Product(s) and its/their suitability for use at the primary health care settings in developing countries. At the conclusion of the testing and evaluation process, WHO will report the results thereof to the Company and, at the Company’s request and cost, return or destroy the
Information and any unused quantities of the Product(s). For the avoidance of doubt, "Information" as used herein does not include the data and information resulting from the testing and evaluation process (including the stability test(s) performed by the Company and submitted to WHO as part of the Product Testing Programme), any other testing results and the reports generated as a result of this Agreement (all the foregoing hereinafter jointly referred to as "the Testing Results"). Such Testing Results shall belong to WHO (subject always, however, to the other provisions of this Agreement).

(2) If and to the extent that the Information has been marked by the Company as "Confidential", WHO shall treat such Information as confidential and proprietary for a period of five years after disclosure to it. In this connection, WHO shall take all reasonable measures to ensure that the Information in question is not used for any purpose other than the aforementioned evaluation and testing activities and is not disclosed or provided to any person who is not bound by similar obligations of confidentiality and restrictions on use as contained in this Agreement.

(3) WHO shall not be bound by any obligation of confidentiality or restriction on use to the extent it is clearly able to demonstrate that any part of the Information:

a) was known to WHO prior to any disclosure by the Company to WHO; or
b) was in the public domain at the time of disclosure by the Company to WHO; or
c) becomes part of the public domain through no fault of WHO; or
d) becomes available to WHO from a third party not in breach of any legal obligations of confidentiality to the Company.

(4) The Company undertakes to abide by similar obligations of confidentiality and restrictions on use as contained in paragraphs 2 and 3 above with regard to the Testing Results (regardless of whether or not such Testing Results have been marked as "confidential").

(5) The provision of Product(s), Information, and Testing Results shall not in itself be construed as conveying rights under any patents or other intellectual property which either Party may have or may hereafter obtain.

(6) Subject to the protection of each Party’s confidential information and the provisions of this paragraph 6, Testing Results may be published by either Party. In order to avoid prejudicing confidential information of the other Party, the submitting Party will transmit to the other Party for its review, the material intended to be published at least 30 (thirty) working days before a proposed publication is submitted to any editor, publisher, referee or meeting organizer. In the
absence of an objection by the other Party within the 60-day period concerning prejudice to its confidential information, and provided that all other conditions of this paragraph 6 have been met, the publication may proceed.

In connection with the foregoing, it is understood and agreed that notwithstanding any other provisions in this Agreement, WHO shall be entitled to evaluate and publish the Testing Results, and to exclusively control this evaluation and the content of the aforesaid publication, provided that in order to avoid prejudice to the Company’s confidential Information disclosed to WHO pursuant to paragraphs 1 and 2 above, WHO shall submit any proposed publication to the Company for review in accordance with the provisions of paragraph 6. For the avoidance of any doubt, the Company shall only be entitled to object to a proposed publication if and to the extent it contains any confidential Information of the Company, and not on the grounds that the Company is not satisfied with the Testing Results and/or does not agree with WHO's evaluation thereof.

The Company shall not proceed to the publication (or any other public disclosure) of any of the Testing Results until such Results have been published by WHO and until the proposed publication has been submitted to WHO for review in accordance with the provisions of paragraph 6.

All publications of the results of any evaluation and testing activities carried out under this Agreement shall include the following statement:

“This investigation was carried out as part of the "WHO Malaria Rapid Diagnostic Test (RDT) Product Testing Programme ".

Other than as provided herein before, neither Party shall, in any statement or material of an advertising or promotional nature, refer to the relationship of the Parties under this Agreement or to the relationship of the other Party to the Product(s). The Company shall not, at any time, use, nor allow any other parties to use, the participation in the Product Testing Programme and/or publication by WHO of the Testing Results for commercial or promotional purposes. Under no circumstances shall the Company or any other party be authorized to refer to WHO, the Company's participation in the Product Testing Programme, and/or the publication of the Testing Results by WHO, in any statement or material of an advertising or promotional nature, press release and/or similar public statement and/or other material aimed at promoting the Company, any other party and/or the Product(s).
(7) The Company shall provide the Information and sufficient quantities of the Product(s) to WHO, or WHO’s designee(s), free of charge. Upon receipt of a written request to that effect, the Company shall furthermore pay any and all costs relating to the evaluation and testing process hereunder to WHO, or WHO’s designee(s), in advance, in accordance with WHO’s instructions. In the event that WHO, or its designee(s), do not receive the Information, and sufficient quantities of the Product(s) by the required deadlines, WHO shall be under no obligation to arrange for the performance of any evaluation or testing activities in relation to the Product(s). Any balance of funds provided by the Company, and remaining unspent upon the conclusion of the testing and evaluation process shall be returned to the Company, unless otherwise agreed by the Parties.

(8) The Company hereby furthermore confirms that it has taken good note of, agrees with, accepts and to the extent applicable, shall abide by, the provisions contained in the document, entitled "Information for Manufacturers on WHO Malaria Rapid Diagnostic Test (RDT) Product Testing Programme."

(9) Any dispute relating to the interpretation or application of this Agreement shall, unless amicably settled, be subject to conciliation. In the event of failure of the latter, the dispute shall be settled by arbitration. The arbitration shall be conducted in accordance with the modalities to be agreed upon by the Parties or, in the absence of agreement, with the rules of arbitration of the International Chamber of Commerce. The Parties shall accept the arbitral award as final.

On behalf of WHO: On behalf of the Company:

Signature: Signature:

Name: Name:

Title: Title:

Date: Date:
## FINAL PRODUCT LIST

**Note:** Please list up to (number to be specified later by WHO-FIND) products, from the list of Expression of Interest (EOI) already submitted to WHO.

(Please note that details of products in this form should have previously been submitted to WHO (Form 1), and that no new product submitted in this form can be accepted for this round of testing).

<table>
<thead>
<tr>
<th>Manufacturer Name</th>
<th>Product 1</th>
<th>Product 2</th>
<th>Product 3</th>
<th>Product 4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Product name¹</td>
<td>Catalogue No</td>
<td>Product name¹</td>
<td>Catalogue No</td>
</tr>
</tbody>
</table>

¹ Write precise name as it should appear in WHO publications, include ™ ® etc.

Name: ____________________________  Signature: ____________________________

Designation / position: ________________  Date: ____________________________
FORM 3

Submit this form by email and hard copy to:

Izabela Suder-Dayao
WHO/TDR
20 Appia Avenue
1211 Geneva
Switzerland
Tel: +41 (22) 791 2261
Fax: +41 (22) 7914854

E-mail: suderi@who.int and Malaria_rdt@who.int

Not later than: 2 November 2012
JOINT-SUBMISSION AND JOINT-LISTING OF PRODUCTS

In cases where products with different names are produced on the same production line, a single product may be submitted for testing and identical products may be jointly listed with the results. The manufacturer of the each separate product should submit a completed EOI. (Such co-submission will require a written application from all the companies concerned and provision of evidence that the products are the same (in the form of a letter signed by the entity indicated as manufacturer (assembler), and a letter signed by the entity or entities indicated as owner(s) of the other products listed as identical). (Please fill the Table on the next page).

In this context, 'manufacture' or 'assembly' indicates production of the test to a state in which it is contained in packaging designed to protect it from environmental degradation (i.e. moisture-proof envelope), including conduct of the quality assurance process in place to ensure product quality. The name of the company which is the operator of the site of manufacture or assembly will be indicated in the list of jointly listed products, together with the name of the company or companies owning the identical products.

In the case of jointly listed products, if one product included in a list of jointly listed products is deemed by WHO to warrant de-listing due to poor performance on lot testing, all jointly listed products will be de-listed and require re-application for product testing. Where products are submitted individually for testing, they will be deemed to be independently manufactured and removal from the product list will involve only the product(s) named.3

3 In cases where a product is de-listed due to poor performance, WHO-FIND may require specific lot testing of other products believed to be the same as the de-listed product.
REQUEST FOR JOINT-SUBMISSION AND JOINT-LISTING OF PRODUCTS AS PART OF THE WHO MALARIA DIAGNOSTICS PRODUCT TESTING PROGRAMME

The following products are manufactured under identical conditions at the same manufacturing site, and are considered re-labelled versions of the same product. It is requested that they be listed as such in the publication of the performance results of product testing by WHO.

It is understood that in the event WHO requires a product to be re-tested due to concerns regarding performance, jointly listed products will be considered as identical and will all be removed from the relevant WHO website lists.

### Details of product submitted for testing and manufacturer of submitted product.

<table>
<thead>
<tr>
<th>Name of manufacturer of product submitted for testing</th>
<th>Product Name</th>
<th>Catalogue Number</th>
<th>Plasmodium species targeted&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Target Antigen (s)</th>
<th>Format&lt;sup&gt;2&lt;/sup&gt;</th>
<th>Contact person and designation</th>
<th>Address</th>
<th>Email URL</th>
<th>Contact numbers</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Details of product to be listed as identical (re-labelled)

<table>
<thead>
<tr>
<th>Name of owner / user of re-labelled product name</th>
<th>Product Name</th>
<th>Catalogue Number</th>
<th>Contact person and designation</th>
<th>Address</th>
<th>Email URL</th>
<th>Contact numbers</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Owner of the Product

Signature_______________________ Name _____________________________ Designation / position _________________________

Manufacturer of the Product

Signature_______________________ Name _____________________________ Designation / position _________________________
NOTE:

A separate signed letter must be provided by the manufacturer submitting product for testing, and the manufacturer/owner of the re-labelled product. Manufacturer requesting for joint submission of a product should send the Expression of Interest (Form 1) and Form 4 by 24 September, 2012.
In reply please refer to:

Your reference:

16 November 2012

Dear Manufacturer,

Re: Round 5 of WHO Malaria RDT Product Testing Programme

1. **Confirmation of final list of products**

   We wish to confirm the acceptance of the following products for inclusion in WHO Malaria RDT Product Testing Programme - Round 5.

<table>
<thead>
<tr>
<th>Product name</th>
<th>Product code</th>
</tr>
</thead>
</table>

2. **Evaluation of future testing methods based on recombinant antigens**

   Evaluation of RDTs in WHO Malaria RDT Product Testing programme is entirely based on the use of cryo-preserved wild type P. falciparum and P. vivax parasites. This will remain so for Round 5. The collection and characterization of these parasitized samples is expensive and prevents the programme from allowing manufacturers to access the same samples as are used in the product testing and lot-testing evaluations. The Programme has been engaged in identification, synthesis, and characterization of recombinant antigens suitable for evaluation of malaria RDTs for over the past 5 years, with the aim of increasing standardization of evaluations and enabling common standards to be available to manufacturers, the evaluation programme and country programmes (for local quality control). These panels will also reduce costs of evaluations, and increase flexibility, reducing the time manufacturers need to wait to have products evaluated. It is intended they will eventually be incorporated into product testing, lot-testing, and the development of Positive Control Wells (PCWs) (suitable for monitoring of RDT quality at a village level). Before introduction, the use of recombinant antigens will be subject to extensive equivalence testing (comparison to the current parasite-based panels). The results of pilot use, and the way they are incorporated into the RDT evaluation process, will be subject to extensive consultation with stakeholders, including RDT manufacturers.
To this end, we are requesting that you voluntarily include an additional 500 RDTs from each lot in your Round 5 shipment. These will be used only in the evaluations of candidate recombinant antigens, to ensure that any future recombinant panels have similar activity on RDTs as the current parasite-based samples, and any future antigen-based system will provide a fair and appropriate evaluation of submitted product. The total requirements, including Round 5 Product Testing and recombinant antigen equivalence testing is 1100 tests. Adding this optional 500 tests will mean 1600 RDTs from each of two lots are shipped.

The results of recombinant testing will NOT be published and are purely for internal use.

3. **Shipment of RDTs to CDC, Atlanta**

Detailed instructions for shipment of RDTs are included in Annex 1. Products must arrive at the CDC, Atlanta by 14 January, 2013. Confirmation of receipt will be sent via email.

4. **Temperature monitors for RDT Shipments (OPTIONAL)**

To request a temperature monitor, send an email to: suderi@who.int with a copy to Malaria_rdt@who.int

Temperature monitors will be shipped in specially formatted envelopes the week of 10 December, to requesting parties.

Instructions on how to fill in the required information on the envelopes is included in Annex 2 (enclosed).

5. **Reminder - obtaining panels of cultured parasites (P. falciparum) for preliminary testing of products by manufacturers (OPTIONAL)**

The manufacturer’s panels are still available. To request a panel, the company must complete and follow instructions outlined in Annex 3 (enclosed).

Panels are provided free of charge, but the manufacturer is responsible for organizing and paying the costs of courier, and organizing all passage through ports and customs once the sample has left the production site at the United States Centre for Disease Control and Prevention (US CDC) in Atlanta, USA. Samples should be shipped on Dry Ice (-78°C). The courier company needs to liaise with Jeffrey Glenn of Centre for Disease Control and Prevention (CDC), Atlanta, USA (khi2@cdc.gov) for arranging the schedules of pick up of the parasite dilution samples. Loss or spoilage of shipments is the responsibility of consignee, and the shipper engaged by the consignee. Due to the limited number of available samples, WHO can not guarantee that spoilt or lost shipments will be replaced.

6. **Manufacturing site thermal stability testing (OPTIONAL)**

As per recommendations in 2010, performance of on-site thermostability evaluation of the submitted lots by the manufacturer using a reference sample and SOP provided by the programme is OPTIONAL. Participation and submission of these results to WHO is no longer required.
However, should a manufacturer wish to continue to follow these procedures using the reference sample from US CDC, and stocks are sufficient, will be made available. Further information is enclosed in Annex 4 including a cover note, stability test protocol and results template.

Please don’t hesitate to contact me should you have any questions or concerns.

Sincerely,

Dr Jane Cunningham
Technical Officer
WHO Global Malaria Programme
World Health Organization
SOPS FOR TRANSPORTATION OF PRODUCTS TO US CDC

1. WHO has a limited number of temperature monitoring devices that can be requested on a first come, first serve basis, to accompany products shipments to CDC, USA. These must be requested via email to suderi@who.int with a copy to Malaria_rdt@who.int

2. The temperature monitor cover envelope must be duly filled in by the manufacturer according to the instructions in Annex 2 of this letter.

3. Temperature monitor should be placed with the cover envelope inside with the RDT products during transportation.

4. Appropriate number of products, **1100 RDTs from each of two lots and 500 optional to support evaluation of recombinant panels under development (total 1600)** for each product listed on the final products list must be submitted to Centre for Disease Control and Prevention (CDC), Atlanta, USA, by 14 January 2013.

Shipping address:
Jeffrey Glenn
Malaria Branch, Division of Parasitic Diseases and Malaria
Centers for Disease Control & Prevention
Bldg. 23, Room 10-169 Mailstop D-67
1600 Clifton Road
Atlanta, GA 30329 USA
Tel: 404.718.4427
Email: khi2@cdc.gov

5. It is **advisable** to use the phrase "These Malaria RDT kits are for in vitro diagnostic use in humans and not for use in animals. These kits are for evaluation purposes by US CDC under the WHO Malaria RDT Product Testing Programme Round 5. These will not be used for any in vitro diagnostic purposes within the territory of United States of America" on the RDT courier boxes being transported to US CDC to minimize the custom issues.

6. In cases of unexpected custom issues or other delays, please inform WHO (cunninghamj@who.int and suderi@who.int ) and provide proof of products leaving manufacturing site before the deadline, other related correspondence, courier tracking numbers etc. These special situations will discussed with WHO-FIND Malaria RDT Evaluation Programme Steering Committee and eligibility for participation in the Programme will be determined and promptly conveyed to manufacturers.

7. Please ensure that final product leaflets previously submitted to WHO-FIND, and those accompanying the RDT shipment are accurate and identical. In the case of any discrepancies, please contact cunninghamj@who.int and khi2@cdc.gov; otherwise the leaflets/instructions accompanying the RDT shipment will apply.
ANNEX 2

TEMPERATURE MONITOR ENVELOPE AND INFORMATION NEEDED

(OPTIONAL)

Please store this envelope together with your malaria rapid diagnostic tests. Complete the form below when this envelope is moved to/from a location.

Date that envelope was placed with RDTs: on the ___/___/___ at ___ h ___.

<table>
<thead>
<tr>
<th>Place (manufacturer name)</th>
<th>Arrival</th>
<th>Departure</th>
<th>Arrival</th>
<th>Departure</th>
<th>Arrival</th>
<th>Departure</th>
<th>Arrival</th>
<th>Departure</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHO</td>
<td></td>
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<tr>
<td>CDC</td>
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<td></td>
</tr>
<tr>
<td>Time (hr. min. Est.: 09:30)</td>
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<td></td>
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<tr>
<td>Type of transport</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Signed</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

NOTE:

1. The temperature monitors are optionally available to manufacturers on a first-come-first-serve basis, free of charge but must be requested via an email to suderi@who.int and copy to Malaria_rdt@who.int
2. The above picture is a sample envelope you will receive containing the temperature monitoring device.
3. The yellow highlighted sections indicate information that manufacturers need to fill in before sending the temperature monitor with RDT products to CDC, USA.
4. Please follow these instructions:
   - Leave the monitor inside this envelope (there is no need to open the envelope).
   - ON THE BACK OF THE ENVELOPE: Fill in the date & time when the envelope was placed in the box of RDT's; (see A above)
   - ON THE BACK OF THE ENVELOPE: Duly fill in the table in order to keep track of the temperature monitor’s location (Arrival + Departure). See B, example above.
   - Please place this envelope safely inside the box together with the RDT’s before the lots are shipped to the Centers for Disease Control and Prevention (CDC) in Atlanta, USA.
ORDER FORM
'MANUFACTURERS PANEL' - CULTURE-DERIVED P. FALCIPARUM SAMPLES
(OPTIONAL)

<table>
<thead>
<tr>
<th>Manufacturer Name</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Manufacturer (consignee) address and email</td>
<td></td>
</tr>
<tr>
<td>Courier company contracted for transport (including full contact details).</td>
<td></td>
</tr>
</tbody>
</table>

Note: It is entirely the manufacturer’s responsibility to contract the shipping agent (courier) and undertake all necessary payments for transport, including supply of packaging materials and dry ice. The manufacturer should be experienced at transporting goods on dry ice (-78°C). Note that the consignment contains dead malaria parasites in human blood:

Category B Biological Substance - UN 3373
Human Blood Samples (Frozen) containing dead malaria parasites
Quantity: 150 vials containing 50 μL
For Laboratory Testing Only
Human material containing no animal material and not of tissue culture origin.

The shipping agent (courier) MUST contact CDC (see details below) beforehand to arrange pick-up of samples. US CDC has the discretion to vary the preferred pick-up date.

Contact details for ordering panels:

<table>
<thead>
<tr>
<th>Order by email:</th>
<th>Jeff Glenn : <a href="mailto:khi2@cdc.gov">khi2@cdc.gov</a></th>
</tr>
</thead>
<tbody>
<tr>
<td>cc:</td>
<td><a href="mailto:vom9@cdc.gov">vom9@cdc.gov</a>; <a href="mailto:Malaria_rdt@who.int">Malaria_rdt@who.int</a></td>
</tr>
</tbody>
</table>

Contact details for courier:

<table>
<thead>
<tr>
<th>Consigner address for courier</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jeffrey Glenn</td>
</tr>
<tr>
<td>Malaria Branch, Division of Parasitic Diseases and Malaria</td>
</tr>
<tr>
<td>Centers for Disease Control &amp; Prevention</td>
</tr>
<tr>
<td>Bldg. 23, Room 10-169 Mailstop D-67</td>
</tr>
<tr>
<td>1600 Clifton Road</td>
</tr>
<tr>
<td>Atlanta, GA 30329 USA</td>
</tr>
<tr>
<td>ph: 404.718.4427</td>
</tr>
<tr>
<td>Email: <a href="mailto:khi2@cdc.gov">khi2@cdc.gov</a></td>
</tr>
</tbody>
</table>
INFORMATION PACK ON MANUFACTURING SITE STABILITY TESTING

(Optional)

This note outlines recommendations for 'optional' manufacturing site stability testing of malaria RDT products submitted for WHO malaria RDT product testing. The testing process is detailed in SOP 2.2 of the Methods Manual of Product Testing v.6\(^1\) (SOP 2.2.d), and a standard report form is provided in electronic format and hard copy. Please keep this note with SOP 2.2.d for future reference.

The stability testing protocol is intended to provide real-time data on thermal stability at the maximum specified temperature recommended for each product, for the duration of the recommended shelf-life, against standardized reference parasite-positive blood samples.

Production lots to be tested

The manufacturing site stability test should be performed using the same production lots as those submitted for product testing to the US Centers for Disease Control and Prevention (CDC), Atlanta, USA. If this is not possible, two other lots of the same product should be used.

Duration of Testing

Testing should continue every 3 months until the expiry date of each lot of RDTs.

Recording and Reporting Results

The line intensity should be rated using the colour intensity rating scale provided by WHO. The colour chart closest to the colour of the RDT test lines should be selected, and used throughout. Note that the intensity rating is not intended to compare visibility of lines between products, but to allow a reduction in intensity over time to be noted.

Results can be optionally communicated to WHO-FIND every 3 months by email attachment to cunninghamj@who.int in the format provided and to Malaria_rdt@who.int

Blood Reference Standard (Obtaining, and use of)

The reference standard is a culture-derived parasite *P. falciparum* parasite sample (Nigeria XII) which forms part of the phase 1 testing panel of the product testing programme and is the standard used for the thermal stability component of the product testing at CDC in Atlanta, GA, USA.

CDC will provide sufficient aliquots of the parasite sample to test two lots of the products of each manufacturer, using the blood volume specified in the manufacturer's product instructions. Blood aliquots should be discarded after use, and not re-frozen.

\(^1\)http://www2.wpro.who.int/internet/resources.ashx/RDT/docs/pdf_version/rdt_laboratory_qc_testing_meth_man_v6.pdf (accessed 14 November 2012)
The samples are provided as 50 μL aliquots in dilutions of 200 parasites/μL and 2000 parasites/μL. If the 200 parasites/μL dilution does not produce a positive test result on initial testing, this dilution may be excluded from the subsequent test at 3 monthly intervals, and the dilution of 2000 parasites/μL alone used.

The blood sample must be obtained from US CDC at the manufacturers expense. The samples must be transported frozen (on dry ice, -78°C) and stored at least at -20°C after receipt.

Please note that the samples should be transported from CDC by engaging a courier experienced in the transport of blood samples on dry ice, and in the relevant customs clearance involved in such transport. The integrity of the samples during transport and on receipt, and the process of clearing through customs and obtaining relevant national regulatory approvals, is the responsibility of the manufacturer (consignee). WHO and CDC will assist with necessary documentation on request.

The courier should be experienced at transporting goods on dry ice (-78°C). Note that the consignment contains dead malaria parasites in human blood:

**Category B Biological Substance - UN 3373**

**Human Blood Samples (Frozen) containing dead malaria parasites**

**Quantity:** XXX* vials containing 50 μL

**For Laboratory Testing Only**

**Human material containing no animal material and not of tissue culture origin.**

The shipping agent (courier) MUST contact CDC before hand to arrange pick-up of samples and relevant documentation. CDC has the discretion to vary the preferred pick-up date.

**Contact details for obtaining blood samples to be used in stability testing at the manufacturing site:**

<table>
<thead>
<tr>
<th>Order by email:</th>
<th>Jeff Glenn: <a href="mailto:khi2@cdc.gov">khi2@cdc.gov</a></th>
</tr>
</thead>
<tbody>
<tr>
<td>cc:</td>
<td><a href="mailto:vom9@cdc.gov">vom9@cdc.gov</a>;</td>
</tr>
<tr>
<td></td>
<td><a href="mailto:Malaria_rdt@who.int">Malaria_rdt@who.int</a></td>
</tr>
</tbody>
</table>

**CDC will notify the manufacturer when parasite dilutions are ready for shipment.**

**Contact details for courier:** The shipping agent (courier) MUST contact CDC (see details below) beforehand to arrange pick-up of samples. US CDC has the discretion to vary the preferred pick-up date.

<table>
<thead>
<tr>
<th>Consigner address for courier</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jeffrey Glenn</td>
</tr>
<tr>
<td>Malaria Branch, Division of Parasitic Diseases and Malaria</td>
</tr>
<tr>
<td>Centers for Disease Control &amp; Prevention</td>
</tr>
<tr>
<td>Bldg. 23, Room 10-169 Mailstop D-67</td>
</tr>
<tr>
<td>1600 Clifton Road</td>
</tr>
<tr>
<td>Atlanta, GA 30329 USA</td>
</tr>
<tr>
<td>Tel: 404-718.4427</td>
</tr>
<tr>
<td>Email: <a href="mailto:khi2@cdc.gov">khi2@cdc.gov</a></td>
</tr>
</tbody>
</table>

The parasite-negative blood sample necessary as a control in the testing process should be provided by the manufacturer.
STABILITY TEST PROTOCOL

Stability Assessment at Manufacturing Site

PURPOSE
This SOP describes the procedure for stability testing of a Rapid Diagnostic Test at the manufacturing site, using standards provided by the WHO - FIND Malaria Rapid Diagnostic Test Evaluation Programme.

SCOPE
This is an optional procedure which applies to manufacturers participating in WHO Malaria RDT Product Testing Programme.

TESTING PROCEDURE (Refer to Figure 1)

1. General

a) Testing should occur at Day = 0, using 24 RDTs from each of 2 lots (total 48), then 12 RDTs from each of 2 lots (total 24) at each 3 monthly interval for the duration of the manufacturer's recommended shelf life.
   - Test 8 RDTs against 200 parasites/μL
   - Test 8 RDTs against 2000 parasites/μL
   - Test 8 RDTs against negative sample

b) Store sufficient RDTs in the incubator incubator/environmental chamber to allow testing of 40 RDTs (20 per lot) every 3 months for the remaining duration of the shelf-life designated for that product by the manufacturer, and sufficient RDTs at 4°C (2-8°C) to allow testing of RDTs (12 per lot) every 3 months for the remaining duration of the shelf-life.

c) Every three months, test 20 RDTs from each lot stored in the incubator and 12 from each lot stored at 4°C:
   - From 4°C storage:
     - Test 4 RDTs against 200 parasites/μL
     - Test 4 RDTs against 2000 parasites/μL
     - Test 4 RDTs against negative sample
   - From incubator:
     - Test 8 RDTs against 200 parasites/μL
     - Test 8 RDTs against 2000 parasites/μL
     - Test 4 RDTs against negative sample

d) Incubated RDTs should be stored at the maximum storage temperature recommended by the manufacturer.

e) Allow a minimum 3 days to calibrate incubators prior to conducting baseline testing.
f) Incubator temperatures and refrigerator temperatures should be recorded daily on a chart attached to the incubator or closely accessible.

g) Mark days when testing is due at 3 month intervals for remainder of shelf life.

h) RDTs should be stacked in incubators in their normal packaging (boxes / kits), allowing air circulation against at least 2 sides of box, and not in direct contact with walls or floor of incubator.

i) All documentation should be readily accessible if manufacturer site inspections occur.

### Table A: Number of RDTs required per lot for STABILITY TESTING.

<table>
<thead>
<tr>
<th>Test</th>
<th>RDTs required per lot at storage temperature</th>
<th>RDT required per lot at 4°C</th>
<th>Total RDTs (both lots)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>24</td>
<td>48</td>
<td></td>
</tr>
<tr>
<td>Each 3 months</td>
<td>20</td>
<td>12</td>
<td>64</td>
</tr>
<tr>
<td>Expiry date</td>
<td>20</td>
<td>12</td>
<td>64</td>
</tr>
</tbody>
</table>

Example for 2 year shelf-life, 3 month old lot when testing commences:

<table>
<thead>
<tr>
<th>Test</th>
<th>RDTs required per lot at storage temperature</th>
<th>RDT required per lot at 4°C</th>
<th>Total RDTs (both lots)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>24</td>
<td>48</td>
<td></td>
</tr>
<tr>
<td>6x3 months</td>
<td>120</td>
<td>72</td>
<td>384</td>
</tr>
<tr>
<td>Expiry date</td>
<td>20</td>
<td>12</td>
<td>64</td>
</tr>
<tr>
<td>Spare</td>
<td>20</td>
<td>12</td>
<td>64</td>
</tr>
<tr>
<td>Total per lot</td>
<td>184</td>
<td>96</td>
<td>560</td>
</tr>
</tbody>
</table>

2. Preparation of product and sample

a) Blood samples to be used as the positive standard for testing are supplied from WHO / CDC (manufacturer must arrange and fund courier), in aliquots of 200 parasites/microL and 2000 parasites/microL, and should be stored at ≤-20°C.

b) Test in air-conditioned (low humidity) environment, at ≤25°C with good lighting.

c) Thaw sufficient aliquots of blood samples designated for RDT stability testing for 30 minutes at room temperature (<30°C) (Each aliquot is approximately 50 microL, so for RDTs requiring 5 uL blood, it is recommended to thaw 3 samples)

d) Store samples aliquots at 4°C after thawing

e) All blood samples must be used within 8 hours of thaw. Do not re-freeze.

f) Withdraw the correct number of RDTs of each lot from storage (incubator and 4°C – Figure 1) and allow to reach room temperature before opening envelope.

g) Test the correct number of RDTs from each lot (diagram below), against aliquots of 200 parasites/microL and 2000 parasites/microL and parasite-negative samples. (If all RDTs have failed at 200 parasite/microL at a previous testing interval, this aliquot may be removed from the testing procedure at future testing intervals. Follow manufacturer's RDT preparation procedure for each product, using pipette or manufacturer's blood transfer device to obtain correct blood volume.

h) If both lots of a product fail to detect the 200 parasites/microL sample at the initial test, the 200 parasite/µL sample may be excluded from future testing and subsequent tests at 3 month intervals conducted using the 2000 parasites/microL sample only.
3. Reading and reporting results

a) Read result within the time period specified by manufacturer, rating line intensity 0-4 against colour intensity chart provided (Use colour closest to colour of positive line). (Colour intensity charts sent to you by courier with other hard copies)

b) Record on the record sheet provided in hard copy and electronic copy.

c) Optionally submit results to WHO-FIND at the specified intervals.

d) Submission of results may cease once all RDTs have failed at any testing interval.
Select sufficient RDTs of each of 2 lots to test:
20 RDTs initially,
32 RDTs at 3 month intervals throughout shelf-life, and at end of shelf life.
It is advised to add at least 64 additional RDTs to allow for errors in process.

Figure 1: Stability Test Flowchart
3. Stability Test Result template

Form 036a: STABILITY TEST: MANUFACTURER’S RESULT SHEET

Manufacturer:
Product:
Lot:

TIME OF READING (INTERVAL IN MONTHS) (’0’, or ’3’, ’6’ etc):
Technician (Name ……………………………………)  Colour chart used:

<table>
<thead>
<tr>
<th>Parasite density: Negative, 200, 2000 para/μL</th>
<th>Time of preparation</th>
<th>Time of reading</th>
<th>Result: Rate colour intensity 0-4 using colour chart provided</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Line 1</td>
<td>Line 2</td>
</tr>
<tr>
<td>Negative</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td></td>
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<td>Negative</td>
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<td>Negative</td>
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<td></td>
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<tr>
<td>Negative</td>
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<td></td>
<td></td>
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<tr>
<td>200 para/μL</td>
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<td></td>
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<td>200 para/μL</td>
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<td>2000 para/μL</td>
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<td></td>
</tr>
<tr>
<td>2000 para/μL</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Result should be recorded according to intensity of line, referenced against ‘colour rating chart’ provided.

‘Control’: Control line. ‘Line 1 -3’: Test result lines, as appropriate for the product.

Signed: ………………………………………