Harmonization of rapid diagnostic tests for malaria and implications for procurement

26–27 February 2015 Geneva, Switzerland
Meeting report
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Background

Over the past 2 years, the WHO Global Malaria Programme (GMP) has been working with the Roll Back Malaria Secretariat, the Roll Back Malaria Procurement and Supply Management and Case Management working groups and partners and the Institute of Tropical Medicine, Antwerp, to review the comparability of malaria rapid diagnostics tests (RDTs) and their compliance with international standards and best practice for labelling and instructions for use (IFU).

The objective was to determine how malaria RDTs could be harmonized to increase their inter-changeability and ease of use and to reduce the burden of retraining and the risk of operator errors when products are replaced or switched in health care settings. This review covers design, packaging, labelling, IFU and the main procedural characteristics (including blood volume, buffer volume, interpretation, reading time). International standards, regulatory documents and published literature were reviewed to identify best practices in these areas.

The initial outputs of the exercise were reviewed and discussed by a large group of stakeholders, including manufacturers, “implementers” and regulatory experts, in December 2013, and subsequently amended, refined and recently published by a “harmonization task force”. To complement the review, additional analyses were conducted to determine variation and similarities in the procedural characteristics of RDTs submitted to rounds 1–5 of the WHO malaria RDT product testing programme.

The stakeholders and the subsequent harmonization task force recommended harmonization of the labelling of the device, boxes and accessories and of the language and format of the IFU. The task force did not make any recommendations about procedural characteristics, such as RDT buffer volume or reading time, but classified these as “outstanding”, for further discussion on specifications and feasibility.

WHO recognizes that building on this comprehensive work could promote compliance with best practices in product labelling and packaging, and thus facilitate RDT procurement, deployment and ease of use. To this end, WHO/GMP held a stakeholder consultation to: review the outputs of the harmonization task force, to make recommendations on requirements for labelling and IFU and to discuss how to encourage compliance with best practices. Items classified as outstanding by the task force were also discussed. The agenda of the consultation is in Annex 1.
The participants included representatives from relevant constituencies: (i) the main bodies involved in RDT procurement (UNICEF Supply Division, the President’s Malaria Initiative, the World Bank, the Global Fund, John Snow International, Médecins Sans Frontières); (ii) regional and national regulatory authorities; and (iii) technical advisory groups (the Foundation for Innovative Diagnostics and the WHO Secretariat, in particular GMP and the WHO programme for prequalification of in vitro diagnostics). Representatives from eight RDT manufacturers attended as observers on the first day of the meeting. Four invited representatives of national malaria control programmes were unable to attend due to unforeseeable circumstances and budgetary constraints, and only one implementing agency (Médecins Sans Frontières) was invited, owing to budgetary constraints. The list of participants is in Annex 2.

The purpose of the report is to provide a succinct summary of the meeting and the recommendations on RDT terminology, packaging and labelling. Verbal and written feedback on the IFU was obtained from participants outside the plenary sessions because of time restrictions.

1. INTRODUCTION, OBJECTIVES AND AGENDA

Jane Cunningham, WHO/GMP

Participants were welcomed, and the absence of national malaria programme representatives was noted and explained. The background to the meeting was presented and the objectives reviewed:

- to agree to any changes required to RDT terms, labelling and IFU proposed by the harmonization task force;
- to determine which of the proposed recommendations should be included in the current WHO recommendations for malaria RDT procurement;
- to agree on a timetable for these changes to take effect;
- to discuss how best to monitor compliance with the recommendations; and
- to further discuss issues for which consensus was not reached and some emerging issues: harmonization of specimen collection devices, lancets, the desiccant, single-use buffer vials and procedural characteristics.

2. OPPORTUNITIES FOR HARMONIZATION: EXPERIENCE OF THE ROLL BACK MALARIA PROGRAMME

Jan Jacobs, Institute of Tropical Medicine, Antwerp

The involvement of the Institute of Tropical Medicine, Antwerp, in the review of RDT characteristics over the past 2 years was described. The process so far has included:

- a desk review of the similarities and differences of 37 RDTs voluntarily submitted to the Institute of Tropical Medicine by manufacturers;
- compilation of international standards, regulatory documents and published literature containing specifications and/or recommendations for RDT design,
packaging and labelling of in vitro diagnostics (which include RDTs), and a questionnaire-based survey of RDT manufacturers and implementers; and

- a Roll Back Malaria stakeholder meeting to review findings on the first two topics and agreement on recommendations on terms, labelling and IFU. Of the 66 recommendations that emerged, 75% were on labelling, of which 75% were extracted from ISO standards and stringent regulatory authority documents. The remaining recommendations were based on the review of the published literature and interviews and discussions with implementers.

The findings and recommendations were published in *The Malaria Journal*.

Guidance on how the recommendations could be put into practice were presented, which included a “blue box”: a generic package incorporating labelling recommendations and some generic instructions for use.

The full presentation is included as Annex 3.1.

### 3. WHO PRODUCT TESTING OF MALARIA RDTS AND CURRENT PROCUREMENT RECOMMENDATIONS

*Jane Cunningham, WHO/GMP*

The WHO malaria RDT product testing programme, which forms the basis for the current recommendations for RDT procurement, was presented. It was noted that the focus of the evaluation programme is diagnostic performance and, while it includes recording basic test characteristics, it does not include an assessment of accessories, IFU and labelling formats. Once recommendations on RDT harmonization are finalized, the product testing programme will also assess adherence to the recommendations. A checklist is being pilot tested on products submitted to round 6 and will become a formal part of product testing from round 7 onwards.

The following points were raised during the discussion.

- The timing of product testing – from publishing a call for expressions of interest to publication of the report of that round – is 16–18 months.

- National regulatory requirements supersede any international recommendation on RDT formats. The difficulties of national registration were recognized.

- Efforts are being made to work directly with national regulatory authorities, such as through the Pan African Harmonization Working Party on Medical Devices and Diagnostics, to work with them in adopting these recommendations as national requirements for registration and, additionally, to facilitate registration of WHO-prequalified products.

The full presentation is included as Annex 3.2.
4. WHO PREQUALIFICATION OF IN VITRO DIAGNOSTICS (PQDX) AND THE MALARIA RDT PIPELINE

Helena Ardura-Garcia, WHO PQDx Team

WHO prequalification of in vitro diagnostics was described, including the assessment procedures. The PQDx programme assesses adherence to international regulations and requirements. It already includes an assessment of products against recommendations proposed by the harmonization task force, and additional recommendations could readily be included into the PQDx dossier assessment and site inspection. In general, the PQDx programme does not enforce recommendations that are not mandated by ISO or other international regulations. The programme and procurement requirements may provide an alternative for enforcing particular recommendations.

The following points were raised during the discussion.

- The PQDx process was recently modified to reduce assessment time. This depends largely on the quality of the dossier submitted, and individual timelines are defined once a product has been submitted. For most products, however, the process takes approximately 12 months.

- There are currently five prequalified malaria RDTs (four P. falciparum-only tests and one combination RDT (Pf/pan) from three manufacturers; additional applications for PQDx are being sought. The PQDx team uses the latest WHO product testing programme to select RDTs that meet the recommended diagnostic performance and contacts the manufacturers to submit to PQDx. Nine malaria RDTs from five manufacturers are under review in the PQDx.

- Data are requested from manufacturers (e.g. clinical studies, field studies, performance), and the results of WHO RDT product testing constitute the laboratory evaluation component of PQDx. A product must meet minimum performance criteria in WHO RDT product testing to be eligible for prequalification.

The full presentation is included as Annex 3.3.

5. RECOMMENDATIONS AND TIMELINES FOR IMPLEMENTATION: TERMS, LABELLING AND IFU

Jane Cunningham, WHO/GMP; Jan Jacobs, Institute of Tropical Medicine, Antwerp

Two documents were reviewed by the group and amended by consensus:

- WHO draft suggested terms and abbreviations related to malaria RDTs; and

- WHO draft suggested requirements for the labelling of malaria RDT kits, including the box, the packaging, the cassette, the buffer, the desiccant and accessories.

The revised versions of these documents represent the main output of this meeting and are included below, with a summary of the discussions that led to the modifications.
Most of the recommendations from the Roll Back Malaria–Institute of Tropical Medicine stakeholder consultation on harmonization of malaria RDTs (3–5 December 2013) were retained. Some were modified to improve their clarity, accuracy or internal consistency, and others were deleted because they were considered irrelevant. Some issues, summarized in point iii below, require additional review and follow-up, with specific documents or expert groups for input. Additionally, WHO/GMP and the WHO PQDx programme will reach consensus on which items for harmonization will be WHO requirements and which will be preferences; this final list will be made publicly available. Furthermore, all pre-existing forms will be adapted to align with these recommendations, and any new materials will respect them.

The recommendations and timelines for compliance discussed and agreed at the meeting are listed below. Most of the recommendations are extrapolated from documents issued by ISO or the International Medical Device Regulators Forum, European Commission directives, US Food and Drug Administration regulations on labelling of in vitro diagnostics and the GP42–A6 guidelines (Procedures and devices for the collection of diagnostic capillary blood specimens) from the Clinical Laboratory Standards Institute (CLSI) and WHO prequalification dossier requirements. Manufacturers should comply as soon as possible; at the latest, all modifications should be made within 2 years of publication of the final recommendations. This grace period allows time for changing and aligning manufacturing processes and the procedures for complete notification of product variation required by various national regulatory authorities for products that are already registered.

Generally, the manufacturers confirmed that changes in terms, labelling or packaging would be addressed together, rather than step-by-step. All modifications in and of themselves or as they affect manufacturing procedures will be associated with increased expense, which will be transferred to the overall cost of the finished products.

- Compliance with IFU will be the simplest to implement, and manufacturers should be compliant within 1 year of publication of the WHO recommendations and templates.

- Modifications to labelling of buffer bottles and cassettes could entail significant changes in manufacturing processes, affecting not only malaria RDTs but also other products in the manufacturer’s product line; similarly, changes to labelling of accessories will require time, as these are often obtained from external suppliers. Therefore, current suppliers will also have to become compliant or other suppliers identified, and the accessories properly validated.

  - Despite the complexities and potential revisions to procedures involved in modifying buffer bottle labels to conform with the original recommendation that both product name and product code appear on the buffer label, there was consensus that users must be able to link the correct buffer to the test (and vice versa). Therefore, preferred and acceptable options are proposed (see section 4, Labelling of the buffer bottle).

The consensus was that manufacturers should be compliant within 2 years of publication of the WHO recommendations and templates.
Additional follow-up with specific documents or relevant groups for input is required for the following:

- how long manufacturers should be required to keep a warning sticker indicating a procedural change visible on the RDT box;
- the permissibility of excluding the list of contents on the RDT cassette packaging if there is insufficient space; and
- preferred and acceptable requirements for labelling buffer bottles with the product name and product codes.

Because of time constraints, participants were invited to review the proposed list of abbreviations and the generic template for IFU and asked to provide any comments or suggested revisions to Jane Cunningham at WHO/GMP. Furthermore, conference calls or, if these are not possible, an e-mail forum will be arranged to consolidate feedback on the IFU with manufacturers, regulatory experts, implementers and procurers.

6. HARMONIZATION OF RDT PROCEDURAL CHARACTERISTICS

Y.S Hong, Access Bio

The speaker described the mechanism of action of antigen-detecting malaria RDTs, including the factors that can be adjusted to optimize test performance. Manufacturers would face technical challenges if RDTs were harmonized for specific procedural characteristics, such as the order of test lines, blood volume, buffer volume and reading time. Furthermore, some of these changes could result in a “new” product, which would require resubmission for registration and prequalification; this would not be achievable within a short time. Others might only have to be notified to PQDx.

In principle, the number of buffer drops could be harmonized by changing the aperture size on the nozzle to deliver the required volume in a defined number of drops. The technicalities of, for example, the options for drop sizes and the potential repercussions on buffer well design, have not yet been considered. Alternatively, individual buffer vials with the volume of buffer required for performing a single test could be provided, if the issues of stability and variable fill associated with the items currently on the market are resolved. Manufacturers are currently obtaining and validating alternative plastics and packaging options for single-use buffer vials.

The full presentation is included as Annex 3.4.

Additional consultation is required to determine the feasibility of harmonizing procedural characteristics, initially exploring the harmonization of buffer drops. Human and financial resources must be identified to support such consultation and subsequent monitoring of progress.
7. CURRENT ALIGNMENT AND MISALIGNMENT OF RDT PROCEDURES AND LABELLING PRACTICES

Theodoor Visser, Clinton Health Access Initiative

An analysis was presented of the range of procedural and labelling characteristics of RDTs that have met WHO procurement criteria in WHO product testing, with sub-analysis of the products of the current nine market leaders. The analysis shows that adoption of the labelling recommendations being discussed by the group would require considerable changes in most RDT products on the market, as few adhere to these recommendations. The procedural characteristics analysed were the number of buffer drops, blood volume and reading time. The results showed that most tests fall into one or two categories, rather than a wide range of combinations. For example, 85% of tests require either two or four drops of buffer, and 85% of tests require 15 or 20 min reading time. Furthermore, many products meet the WHO procurement criteria and have the same requirements for buffer drops and reading times (see Figure 1).

Although there is no general consensus on the number of products necessary for open competition, these findings indicate that countries that have a strong preference for retaining a test with similar procedural characteristics to obviate retraining and the risk of operator errors could issue tenders for a limited range of products.

If the rules of open competition cannot be respected with the current selection of high-performing, interchangeable products, retraining can have positive outcomes, especially where routine supervision, outreach training supervision support and refresher training, prompted by supervision, are poor.

The full presentation is included as Annex 3.5.

**FIGURE 1.**
Harmonization of procedural steps – Combination of reading and buffer quantity for Pf and Pf/Pan RDTs that meet WHO procurement criteria

<table>
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<td>Out of all 31 RDTs that require 20 minutes</td>
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<tr>
<td>• 58% of tests require 2 drops</td>
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<tr>
<td>• 26% of tests require 4 drops</td>
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<tr>
<td>Out of 13 Pf/Pan tests, 43% of tests require 2 drops and 29% 4 drops</td>
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<tr>
<td>Out of 26 Pf only tests, 50% of tests require 2 drops and 33% 4 drops</td>
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<tr>
<td>All 15 RDTs that require 15 minute waiting time: 67% requires 4 drops and none of these RDTs require 2 drops</td>
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<tr>
<td>Both 2 Pf/Pan tests require 4 drops</td>
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<td>Out of 9 Pf tests, 4 tests require 4 drops, 2 tests require 3 drops and 2 tests require 5 drops</td>
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8. ALTERNATIVE SOLUTIONS TO FACILITATING PROCUREMENT AND REDUCING ERRORS AND RETRAINING

Jane Cunningham, WHO/GMP

Three other approaches for supporting countries in procurement and reducing the impact of non-alignment among RDTs were outlined.

- Better use of available data
  The procedural characteristics of all products undergoing WHO product testing are recorded, and the data could be made more accessible. In particular, the Foundation for Innovative Diagnostics interactive guide (database of WHO product testing results) could be adapted to include this information and allow filtering by product characteristic. If countries prefer to procure a product with similar characteristics to the one currently in use, this tool would allow them to identify more easily the available products that have similar or identical characteristics. Procurers and, if appropriate, their donors would have to consider whether the pool of similar products is large enough to make characteristic-specific procurement acceptable.

  Depending on the procurement or funding requirements of an agency, countries might be able to make fairly robust arguments for tendering for tests within a specific range of procedural characteristics, with the rationale that maintaining consistency will reduce the need for and costs of full retraining and document revision, so that they can focus on strengthening the quality of use of current procedures. The analysis presented in section 7 shows that 2–13 products have similar characteristics; therefore, procurement can still be competitive, even if the specifications are extended beyond “performance criteria” to other characteristics.

- Training and supervision
  Targeting training to the features of RDT products that differ, i.e. number of buffer drops, reading time and interpretation, may reduce errors.

- Product development
  New products developed according to the harmonized procedures may help shape the market of the future.

In the discussion, it was noted that harmonizing procedural characteristics and guiding product development by issuing target product profiles with highly specific specifications, such as the number of buffer drops and reading times, might:

- lead to a market dominated by large companies, as tests could become similar in all ways except price; therefore, companies that can manufacture at scale and benefit from the economies would win all the tenders;

- stifle innovation in the industry, as new products would be restricted by the narrow specifications, and developers might consider that the risk of not meeting the “preferred” specifications is too high.

The full presentation is included as Annex 3.6.

The discussions of day 1 were summarized; the presentation is included as Annex 3.7.
9. PROPOSED UPDATED WHO PROCUREMENT CRITERIA

Jane Cunningham, WHO/GMP

It was agreed that no immediate changes would be made but that the next steps will include:

- Publication of a meeting report
- Preparation of a WHO “information note” outlining the recommendations and requirements on terms, labelling and IFU to serve as a guide for manufacturers. For example, some of the proposed measures such as label orientation cannot be included as requirements in PQDx assessment but could be included as suggestions.
- Finalization of assessment tools and checklists for monitoring adherence to the recommendations and requirements during product testing and PQDx
- Expressions of interest for round 7 will include the IFU, labelling and packaging requirements, on which submitted products will be assessed and scored.
- The round 7 report will be the first to include evaluation of products with regard to these recommendations.
- The document “Good practices for selecting and procuring rapid diagnostic tests for malaria” will be modified, and the next version will include the outcomes of this harmonization process.
- As the proposed deadline for full compliance with all recommendations will be 2 years (see section 5), the procurement criteria would be revised at that time. In 2 years, however, others requirements will have to be considered, such as for WHO prequalification, which indirectly covers the labelling and IFU recommendations.
- As there is no consensus on the critical numbers of WHO prequalified products and manufacturers that would allow a healthy, competitive market, GMP should assess the factors that could affect transition to a requirement that only WHO-prequalified malaria RDTs be procured and propose timelines that would allow continued competition, stable prices and limited market disruption.
- Should this assessment support a requirement that only WHO-prequalified malaria RDTs be procured in the next 2 years, there will be many more new PQDx applications in the coming year. The WHO PQDx team confirmed that they are likely to be able to absorb this demand.
- To ensure that products that are already WHO prequalified comply with the recommendations, the PQDx team should have a system for ensuring that all products are fully aligned.

The full presentation is included as Annex 3.8.
10. OUTSTANDING ISSUES

Jan Jacobs, Institute of Tropical Medicine, Antwerp; Jane Cunningham, WHO/GMP

The background document, which describes the outstanding issues that were discussed, is included as Annex 4.

Single packs

Single packs are packages containing all the components and accessories required to perform the RDT: cassette (device), buffer vial, lancet, specimen transfer device, desiccant and IFU. In this document, they are not intended for self-testing.

Discussion point: Should all the recommendations agreed upon also apply to RDT single packs?

Conclusion:
- All recommendations should apply to single packs, and some additional recommendations may be required

Issues discussed:
- In practice, boxes of RDT single packs may be split. Labelling of the pouch is therefore even more important for single packs.
- A recommendation for inclusion of simplified IFU in the single pack should be considered further. They should not be called IFU, as they should not have to adhere to the same regulatory requirements as IFU. “Job aid”, “short operating procedures” or a similar description would be preferred. Their design must be considered carefully, as single packs are used in a range of settings, including communities, low-throughput health facilities and also, at times, high-throughput health facilities.
- Accessories in single pack must be appropriately labelled to allow traceability.
- Vials might be marked to show the volume of buffer; a lower level could indicate evaporation or insufficient filling at the time of manufacture.

Lancets

Discussion point: Should more complex, presumably safer lancets (such as auto-retractable lancets) be recommended rather than traditional lancets?

Conclusion:
- No recommendation for a specific type of lancet is made at this time. A list could be drawn up from available data on the different options, with item prices and the pros and cons of each. This could be included in the next version of the document Good practice for selection and procurement of RDTs for malaria.

Issues discussed:
- The implications of recommending use of more complex lancets should be studied further to determine whether the additional cost is offset by benefits.
• Evidence on the pros and cons of different lancets is limited, including patient and health worker preferences, adherence to safety protocols and total cost implications (item costs plus packaging and shipping costs).

**Transfer device**

**Discussion point:** Should WHO recommend that only inverted cups or loops be used as blood transfer devices for malaria RDTs?

**Conclusion:**
- **No firm recommendation is made at this stage.** On the basis of the two published studies, a preference for the loop or the inverted cup should be stated in the Good practice guide.

**Issues discussed:**
- The accuracy and acceptability of various specimen transfer devices has been addressed in only two published studies. Additional studies on accuracy and user preferences (by different cadres of health worker and capillary drop versus anti-coagulated blood in a tube) and assessment of the compatibility of transfer devices with various RDT sample wells are encouraged.
- WHO PQDx indicated that a change in specimen transfer device would probably require submission only of a notification of variation (including data to demonstrate that the change does not affect performance) rather than a new product submission to PQDx.

**Inclusion of supplemental buffer and accessories**

**Discussion point:** should supplemental accessories and buffer be included with RDTs to avoid shortages in the field?

**Conclusion:**
- Procurement agencies or countries should make decisions on the basis of their experience and mode of use of the tests.

**Issues discussed:**
- Generally, excess buffer is included, but this does not help if a bottle is lost or spilt. The point for discussion is whether spare bottles should be included. Participants said that this could help prevent misuse by ensuring that test users who have run out of or lost the buffer do not resort to “making do” with other buffers or water. Misuse could occur, however, if spare bottles are stored and used for other rapid tests for which they were not intended.
- The estimated cost of including an additional bottle of buffer by one RDT manufacturer would be US$ 0.05 per test (in a box of 25) and another US$ 0.05 for inclusion of additional transfer devices, swabs and lancets. Because of the considerable increase in cost of including an additional bottle, it is unlikely that this practice will be adopted.
- Additional supplies of items that are easily contaminated, such as lancets and specimen transfer devices, would be useful. Extra buffer, although probably prohibitively expensive in most settings, would be useful in multi-user settings.
If any additional items are packaged with an RDT, the product labelling must be modified to reflect the contents, and a new product code should be assigned. Requirements for notification of regulators with and without WHO prequalification would ensue.

An alternative way for procurers and countries to avoid shortages is to procure supplementary accessories separately from safety boxes, gloves etc. It is not clear whether this would be cheaper or more expensive, but it would avoid the issue of multiple product codes.

**Desiccants**

**Discussion point:** Should required specifications for desiccants be established?

**Conclusion:**
- Self-indicating desiccants are not required and would entail additional cost. If there is a self-indicating desiccant and there is evidence that it has been exposed to humidity, the safest approach is not to use the test.

**Issues discussed:**
- Desiccants can play two roles.
  - Most importantly, they absorb any trace of humidity; the user should not have to check the desiccant.
  - If it is self-indicating, the user can check whether the test has been exposed to excess humidity. Generally, the indicator changes only at very high levels of saturation. Specifications for the self-indicating desiccant must be included in the tender request, such as the level of humidity at which the colour changes.
- Barbé et al. found that 4.6% of RDTs had saturated desiccants; however, there was no evidence of an effect on test performance.
- Self-indicating desiccants require visual inspection; assessment may be difficult when only a selection of beads are self-indicating.

**11. UPTAKE AND MONITORING OF COMPLIANCE**

**Chair:** Lawrence Barat, USAID, President’s Malaria Initiative

The ways in which uptake and compliance with these recommendations can be promoted and monitored were discussed.

**WHO product testing checklist**

_Sandra Incardona, Foundation for Innovative Diagnostics_

GMP and the Foundation for Innovative Diagnostics drafted and pilot tested (at the US Centers for Disease Control and Prevention) a checklist for assessing compliance with the recommendations for terms, labelling and IFU. It will be modified to reflect any changes agreed during this meeting. This checklist is intended for use during WHO product testing and will be pilot tested for round 6 products. The results will not
be made public, but individual reports will be sent to manufacturers. After round 7 of product testing, the checklist will be a formal part of the evaluation process. It will be included in the expressions of interest for round 7, to be announced in May 2015.

The full presentation is included as Annex 3.9.

**WHO prequalification dossier**

**Sabine Ohse, WHO PQDx team**

Examples of the checklists currently used were presented; these overlap with the GMP/Foundation for Innovative Diagnostics checklist but are less exhaustive and are more easily generalized to other in-vitro diagnostic tests. PQDx gives guidance to manufacturers on interpreting the requirements, including what is “appropriate” and “legible”.

A sample dossier (for point-of-care CD4 testing, not for a malaria RDT) and guidance for dossier completion are available for submission to PQDx. A sample dossier for malaria RDTs would be extremely useful for this process.

The recommendations made at this meeting should be requirements in the evaluation of product checklists. When this is impossible, it may be appropriate to list them as recommendations. Malaria-specific recommendations (as opposed to requirements) could be annexed to the submission guidelines.

The full presentation is included as Annex 3.10.

**Procurers**

All the procurer present were invited to present their perspectives on how the recommendations might affect their practices.

**World Bank**

**John Paul Clark**

- As a non-technical agency, the Bank relies on technical agencies to provide guidance; only when clear technical guidance is in place would the procurement criteria be changed.

- The Bank uses a quality threshold (in the case of malaria RDTs, it is usually having passed WHO product testing); after that, cost becomes the issue.

- The outcomes of this meeting and the way in which they are applied will be important to the Bank in planning future procurement practices.

- In the medium term, the Bank expects to make WHO PQDx for RDTs a requirement for procurement; however, the implications for competitiveness must be considered and would probably be the main factor in that decision.
**USAID and President’s Malaria Initiative**

**Lawrence Barat**

- The priority of the President’s Malaria Initiative is to provide high-quality diagnostics at the best price, to ensure that the tests are accurate and that national RDT requirements are met.

- For a high-volume, low-cost commodity, even small increases in price can result in a large reduction in the number of units that can be procured in a resource-constrained environment. Even a US$ 0.10 increase in unit cost would represent a 25% increase, reducing the number of RDTs that could be procured with the same money by 20%.

- The President’s Malaria Initiative does not consider that these recommendations will significantly improve either the products or their performance. Instead, the complexity of labelling might create more confusion.

- The Initiative requires strict regulatory authority approval or WHO pre-qualification of drugs. For RDTs, the Initiative has yet to be convinced that pre-qualification will add value beyond that already provided by the WHO product testing scheme.

**UNICEF**

**Bibiana Zambrano, Supply Division**

- UNICEF allows countries to take the lead in choosing tests and does not influence such decisions, except for stating that products must meet WHO procurement criteria (based on WHO product testing results).

- Ensuring that there are more good-quality products on the market will improve competition and drive price reductions.

**Regulators**

**Lawrena Okoro, Medical Laboratory Science Council of Nigeria and Sarvashni Moodliar, National QA Operations and Support, National Health Laboratory Service, South Africa**

- The process adds value to the mechanisms in place in the country; it clarifies the meaning of a product that has been prequalified or been through WHO product testing. It will inform country evaluations of ease of use, performance and product safety, which are of increasing interest.

**12. NEXT STEPS AND ACTION PLAN**

**Jane Cunningham, WHO/GMP**

- WHO/GMP will finalize the documents that were reviewed during the meeting on terms, labelling and IFU.

- Recommendations on IFU were not reviewed in plenary because of time constraints; however, voluntary inputs will be incorporated, and separate conference calls and/or e-mail forums will be established with each stakeholder group for additional feedback.
• WHO/GMP will reach consensus with the WHO PQDx team on which recommendations can be included as WHO requirements and which will be recommendations or preferences.

• Translation of the preferred terms into at least the five other official WHO languages will be a priority.

• The outcomes of this meeting will be disseminated through:
  - publication of the meeting report;
  - publication of a WHO information note with guidance to manufacturers;
  - announcement of round 7 expressions of interest in May 2015; and
  - possible revision of the Good practice guide for selecting and procuring RDTs for malaria.

• Implementation:
  - There will be no immediate change to the procurement criteria.
  - Round 7 will be the first round of product testing in which terms, labelling and IFU requirements will be assessed and the results documented in the product testing report.
  - The deadline at which these recommendations become a requirement for WHO procurement may overlap with a transition to a requirement of WHO prequalification for procurement. WHO/GMP will determine when and how this transition might occur so as to avoid disruption in the market. Manufacturers will be given advance warning of the transition, and WHO PQDx will ensure that it can accommodate an increased demand for review of applications and dossiers.

• Further harmonization:
  - Additional research recommended by this group will be communicated to partners, and discussions will be initiated on some topics.
  - WHO/GMP will discuss internally whether they can assume the task of acting on opportunities to harmonize the number of buffer drops.
Changes made to drafts of suggested standards

The text of two documents follows:

- WHO draft suggested terms and abbreviations related to malaria RDTs
- WHO draft suggested requirements for the labelling of malaria RDT kit components

Points raised and amendments suggested during the meeting are shown in red. Items for action are highlighted in yellow.

**WHO DRAFT SUGGESTED TERMS AND ABBREVIATIONS FOR MALARIA RDTs**

Materials affected:

- Instructions for use
- Labelling of box, cassette, components, accessories
- Job aids
- Promotional materials

**Recommended terms**

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>Abbreviation</th>
<th>Description</th>
<th>Synonym (Not Suggested Term)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Accessories</td>
<td></td>
<td>Articles intended and validated by the RDT manufacturer to be used with the RDT in order to achieve its intended purpose (i.e. specimen transfer device, lancet, alcohol swab)</td>
<td>Ancillary items</td>
<td>The accessories provided might be replaced by other items without compromising safe, accurate performance of the test, e.g. different lancets. This possibility of substitution differentiates “accessories” from “components” (see “Component”). Action item: to determine a term to refer to items that are also required to perform the test correctly and safely but are not included, e.g. timer or watch, gloves.</td>
</tr>
<tr>
<td>Alcohol swab</td>
<td></td>
<td>A pad saturated with alcohol that is used to clean and/or disinfect skin</td>
<td>Alcohol pad, alcohol wipe, alcohol prep-pad</td>
<td>There was consensus that “alcohol swab” is the term in broadest use, both in spoken language and in labelling.</td>
</tr>
<tr>
<td>PREFERRED TERM</td>
<td>ABBREVIATION</td>
<td>DESCRIPTION</td>
<td>SYNONYM (NOT SUGGESTED TERM)</td>
<td>COMMENTS</td>
</tr>
<tr>
<td>----------------</td>
<td>--------------</td>
<td>-------------</td>
<td>-----------------------------</td>
<td>----------</td>
</tr>
<tr>
<td>Auto-transfer cassette</td>
<td></td>
<td>Cassette presenting with an opening which allows direct sampling of the blood on the nitrocellulose strip.</td>
<td></td>
<td>There was consensus that this term should be removed from the list, as it is not of high relevance.</td>
</tr>
<tr>
<td>Buffer</td>
<td></td>
<td>A buffered solution to enable specimen flow and conditioning of specimens, to optimize sensitivity and minimize non-specific reactions.</td>
<td>Many synonyms are in use, e.g. “blood lysis buffer”, “clearing buffer”, “assay diluent”, “sample diluent”, “reagent”</td>
<td></td>
</tr>
<tr>
<td>Buffer bottle</td>
<td></td>
<td>Plastic bottle, often with cap and nozzle, containing the buffer, intended to be used in multiple tests</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Buffer vial</td>
<td></td>
<td>Small vial containing a sufficient volume of buffer to perform a single RDT test. See “primary packaging”</td>
<td>“Buffer ampulla”</td>
<td></td>
</tr>
<tr>
<td>Buffer well</td>
<td></td>
<td>Physical place in the test device in which the buffer is applied.</td>
<td>Some RDTs have a single well for both buffer and specimen.</td>
<td></td>
</tr>
<tr>
<td>Cassette</td>
<td></td>
<td>This is the test format in which the nitrocellulose strip is encased in a plastic housing, presenting openings for the result window, for the specimen and buffer well(s) and in some cases for evaporation.</td>
<td>Commonly referred to as the “device”</td>
<td></td>
</tr>
<tr>
<td>Combination rapid diagnostic test</td>
<td></td>
<td>Test for detecting multiple malaria species and which distinguishes P. falciparum from other malaria species</td>
<td>Commonly referred to as a “combo test”</td>
<td></td>
</tr>
<tr>
<td>Component</td>
<td></td>
<td>Dedicated parts of a finished, packaged, labelled RDT kit that are specific to and necessary for performing the RDT. These include the test device, buffer bottle/vial and instructions for use.</td>
<td>Note: There can be no substitution for a kit component, whereas accessories such as a lancet or alcohol swab may be replaced by items that perform the same function or are purchased separately.</td>
<td></td>
</tr>
<tr>
<td>Control line</td>
<td>C</td>
<td>Visible line on the nitrocellulose strip that indicates satisfactory migration of buffer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Desiccant</td>
<td></td>
<td>Drying agent used to protect the test device from humidity. These may change colour (self-indicating) to indicate humidity saturation. The beads are contained in a transparent, partially transparent or non-transparent fiber pouch.</td>
<td>Silica gel is the most commonly used desiccant for RDT products.</td>
<td></td>
</tr>
<tr>
<td>Dipstick</td>
<td></td>
<td>Test format consisting of only the nitrocellulose strip, which is placed on/in a platform (e.g. tube, backing paper)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Histidine-rich protein 2</td>
<td>HRP2</td>
<td>Malaria antigen expressed by P. falciparum</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PREFERRED TERM</td>
<td>ABBREVIATION</td>
<td>DESCRIPTION</td>
<td>SYNONYM (NOT SUGGESTED TERM)</td>
<td>COMMENTS</td>
</tr>
<tr>
<td>--------------------------------------</td>
<td>--------------</td>
<td>-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>-------------------------------------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------</td>
</tr>
<tr>
<td>In vitro diagnostic medical device</td>
<td>IFU</td>
<td>A device, used alone or in combination, intended by the manufacturer for in vitro examination of specimens derived from the human body, solely or principally to provide information for diagnosis, monitoring or compatibility. They include reagents, calibrators, control materials, specimen receptacles, software, related instruments or apparatus or other articles (International Medical Devices Regulators forum)</td>
<td><a href="http://www.imdfr.org/docs/ghtf/archived/sg1/technical-docs/ghtf-">http://www.imdfr.org/docs/ghtf/archived/sg1/technical-docs/ghtf-</a> sg1-n045r12-in-vitro-diagnostic-classification-070209.pdf</td>
<td></td>
</tr>
<tr>
<td>Instructions for use</td>
<td></td>
<td>Information provided by the manufacturer to the user about the intended purpose and proper use of in vitro diagnostics and any precautions to be taken (GHTF/SG1/n70:2011)</td>
<td>“Package insert”, “instructions leaflet”</td>
<td></td>
</tr>
<tr>
<td>Job aid(s)</td>
<td></td>
<td>Document describing the essential materials to perform an RDT (i.e. procedure or interpretation) provided apart from the IFU, either as a separate leaflet and/or printed on the device packaging or in/on the RDT box</td>
<td>“Quick guide”, “pictogram testing procedure”</td>
<td>Refer to the “WHO generic job aids” for an example.</td>
</tr>
<tr>
<td>Kit</td>
<td></td>
<td>Set of components and accessories packed together and intended for using a specific RDT (test device, buffer bottle, specimen transfer device, lancet, alcohol swab, instructions for use) (definition adapted from ISO 18113-1:2009)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lancet</td>
<td></td>
<td>Sharp, needle-like, sterile medical device used to puncture skin to obtain blood (CLSI H04-A6). They include: • plain metal lancets (packed in a single packages for sterility) • safety-seal lancets (in plastic housing with a plastic cap) • auto-lancing lancets (mounted in plastic housing that is ejected automatically when the plunger is pressed) • auto-retractable lancets (mounted in plastic housing that is retracted automatically after puncture)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lot</td>
<td></td>
<td>Defined amount of material with uniform properties that has been produced in one process or series of processes so that it can be expected to be homogeneous (ISO 18113-1:2009)</td>
<td>“Batch”</td>
<td></td>
</tr>
<tr>
<td>PREFERRED TERM</td>
<td>ABBREVIATION</td>
<td>DESCRIPTION</td>
<td>SYNONYM (NOT SUGGESTED TERM)</td>
<td>COMMENTS</td>
</tr>
<tr>
<td>------------------------</td>
<td>--------------</td>
<td>-----------------------------------------------------------------------------------------------</td>
<td>-----------------------------------------------</td>
<td>-------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Lot number</td>
<td></td>
<td>Distinctive set of numbers and/or letters for a kit or component that specifically identifies a lot and permits tracing of its manufacture, packaging, labelling and distribution history (ISO 18113-1:2009)</td>
<td>“Batch number”, “batch code”</td>
<td></td>
</tr>
<tr>
<td>Malaria rapid</td>
<td>RDT</td>
<td>A collection of reagents and other associated materials for <em>in vitro</em> diagnostics, intended to be used for the qualitative and/or quantitative detection of antigens from one or more species of <em>Plasmodium</em> in a clinical specimen within a short period, relative to standard laboratory testing procedures, typically by an immunochromatographic test method</td>
<td></td>
<td>This test is commonly used in the laboratory or in point-of-care analyses.</td>
</tr>
<tr>
<td>diagnostic test</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Manufacturer</td>
<td></td>
<td>Any natural or legal person with responsibility for design and/or manufacture of a medical device with the intention of making the medical device available for use, under his or her name, whether the medical device is designed and/or manufactured by that person him- or herself or on his or her behalf by another person(s) (GHTF/SG1/N055: 2009 Definitions of the terms “manufacturer”, “authorized representative”, “distributor” and “importer”)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Plasmodium</em> antigen</td>
<td></td>
<td>Antigen* produced by malaria parasites and detected with RDTs</td>
<td>Target, marker, analyte</td>
<td></td>
</tr>
<tr>
<td><em>Plasmodium</em></td>
<td>P</td>
<td></td>
<td></td>
<td>“P” is to be used only as the abbreviation of the genus and in combination with the species name (e.g. <em>P. ovale</em>) or as part of the abbreviations “Pm, Po, Pv, Pf and Pvov”; it should not be used alone.</td>
</tr>
<tr>
<td>pan-</td>
<td></td>
<td>A group of human <em>Plasmodium</em> species: Pf, Pv, Po and Pm</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Plasmodium</em> falciparum</td>
<td>Pf</td>
<td></td>
<td><em>Plasmodium falciparum</em></td>
<td></td>
</tr>
<tr>
<td><em>Plasmodium</em> (or parasite) lactate dehydrogenase</td>
<td>pLDH</td>
<td><em>Plasmodium</em> (or parasite) lactate dehydrogenase</td>
<td></td>
<td>In papers and documents, both “parasite” and “<em>Plasmodium</em>” lactate dehydrogenase are used. In the present context and documents (such as IFU), it would be better to maintain “<em>Plasmodium</em>”</td>
</tr>
<tr>
<td><em>Plasmodium</em> malariae</td>
<td>Pm</td>
<td></td>
<td><em>Plasmodium malariae</em></td>
<td></td>
</tr>
<tr>
<td><em>Plasmodium</em> ovale</td>
<td>Po</td>
<td></td>
<td><em>Plasmodium ovale</em></td>
<td></td>
</tr>
<tr>
<td><em>Plasmodium</em> vivax</td>
<td>Pv</td>
<td></td>
<td><em>Plasmodium vivax</em></td>
<td></td>
</tr>
<tr>
<td><strong>PREFERRED TERM</strong></td>
<td><strong>ABBREVIATION</strong></td>
<td><strong>DESCRIPTION</strong></td>
<td><strong>SYNONYM (NOT SUGGESTED TERM)</strong></td>
<td><strong>COMMENTS</strong></td>
</tr>
<tr>
<td>-------------------</td>
<td>------------------</td>
<td>----------------</td>
<td>----------------------------------</td>
<td>-------------</td>
</tr>
<tr>
<td><em>Plasmodium vivax, ovale, malariae</em></td>
<td>Pvom</td>
<td><em>Plasmodium vivax, ovale, malariae</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Point-of-care testing</strong></td>
<td>POCT</td>
<td>Testing used at or near the site of patient care, leading to a possible change in the care of the patient (ISO 22870 2006)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Primary packaging of alcohol swabs, lancets, desiccant and cassettes</strong></td>
<td></td>
<td>Layer of packaging in immediate contact with the item</td>
<td>Alcohol swab, lancet, desiccant or cassette packaging</td>
<td></td>
</tr>
<tr>
<td><strong>Packaging of alcohol swab, lance, desiccant or cassette</strong></td>
<td>Pouch, sachet</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Product</strong></td>
<td></td>
<td>RDT as currently marketed and identified, with assigned name, product code and regulatory version</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Product code</strong></td>
<td></td>
<td>Unique code identifying one product (or product variant) with an assigned name and a regulatory version</td>
<td>Catalogue number, product number, reference number</td>
<td></td>
</tr>
<tr>
<td><strong>RDT box or Box</strong></td>
<td></td>
<td>Physical box, usually made of cardboard, in which the kit contents (components and accessories) are packed</td>
<td>Secondary packaging, kit box</td>
<td></td>
</tr>
<tr>
<td><strong>Reading legend</strong></td>
<td></td>
<td>Acronyms or characters in the result window, referring to the control and test lines. The characters may be embossed in the plastic housing or printed/glued on it. The reading legend can be on either side of the result window.</td>
<td>Reading scale</td>
<td></td>
</tr>
<tr>
<td><strong>(Minimum and maximum) reading time</strong></td>
<td></td>
<td>Interval during which valid results can be obtained</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Result window</strong></td>
<td></td>
<td>Opening in the test cassette showing the area of the strip containing the control and test line(s)</td>
<td>Reading window</td>
<td></td>
</tr>
<tr>
<td><strong>Revision history</strong></td>
<td></td>
<td>A table in which amendments are recorded each time a new version of the IFU is issued</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Single pack</strong></td>
<td></td>
<td>RDT individually packed with all the content required for the performance of one test</td>
<td>Single test pack, single test, individually packaged test</td>
<td></td>
</tr>
<tr>
<td><strong>Species</strong></td>
<td>spp.</td>
<td>Species</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Specimen well</strong></td>
<td></td>
<td>Physical place in the test cassette or dipstick to which the specimen is applied</td>
<td>Some malaria RDTs have a single well for both specimen and buffer.</td>
<td></td>
</tr>
<tr>
<td><strong>Specimen transfer device</strong></td>
<td></td>
<td>Device used to transfer blood (or plasma or serum) to the test device. This includes: inverted cup, loop, (glass) capillary tube, (plastic) straw, pipette.</td>
<td>Sampling device</td>
<td></td>
</tr>
<tr>
<td><strong>The term “specimen transfer device” may be shortened to “transfer device”</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Symbol key

<table>
<thead>
<tr>
<th>PREFERRED TERM</th>
<th>ABBREVIATION</th>
<th>DESCRIPTION</th>
<th>SYNONYM (NOT SUGGESTED TERM)</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symbol key</td>
<td></td>
<td>List of symbols with written explanation (“legend”)</td>
<td>Key to symbols</td>
<td></td>
</tr>
<tr>
<td>Test line</td>
<td></td>
<td>Line on the nitrocellulose strip that is intended to display the reaction with a specific target antigen (HRP2, pLDH, aldolase)</td>
<td>The term “band” can be used depending on the RDT design (two-, three- and four-band RDT products)</td>
<td></td>
</tr>
<tr>
<td>Test strip</td>
<td></td>
<td>The physical medium, e.g. nitrocellulose, in which the migration and reaction take place</td>
<td>“Test membrane”</td>
<td></td>
</tr>
<tr>
<td>Two-, three- and four-band RDTs</td>
<td></td>
<td>RDTs with two, three or four lines, including the migration control line, and one, two or three test lines</td>
<td></td>
<td></td>
</tr>
<tr>
<td>User</td>
<td></td>
<td>A trained or skilled person who uses the RDT</td>
<td>Operator, end-user</td>
<td></td>
</tr>
<tr>
<td>Version number</td>
<td></td>
<td>Number given to any labelling, including labels, instructions for use (or job aids) or any other materials distributed with the product, to allow tracking of changes.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### WHO DRAFT SUGGESTED RECOMMENDATIONS FOR THE LABELLING OF MALARIA RDT KIT COMPONENTS: BOX, CASSETTE PACKAGING, CASSETTE, BUFFER BOTTLE AND ACCESSORIES

### GENERAL NOTE ON LABELLING LEGIBILITY

There are no international guidelines on font sizes for labels of in-vitro diagnostics.

- According to the *Guideline on the readability of the labelling and package leaflet of medicinal products for human use*, revision 1, 12 January 2009, characters of at least 7 points (or of a size in which the lower case “x” is at least 1.4 mm in height) with a space between the lines of at least 3 mm are recommended.¹⁹

- The US Food and Drug Administration document *Guidance on medical device patient labelling; final guidance for industry and FDA reviewers* (2001), for patients and lay caregivers, recommends use of at least 12-point type whenever possible and a serif font for text.
1. LABELLING OF THE RDT BOX

Orientation:

FIGURE 1.
Convention of terms for the front view of a malaria RDT box

General requirements and preferred options for labelling malaria RDT boxes:

1. **Labels** should be printed on the cardboard as permanent printing or applied as water-resistant labels (applied with water-resistant glue). Printing should be indelible and should last the life span of the RDT product.

2. **Use only internationally recognized symbols** (ISO 15223–2012 or, if applicable, the globally harmonized system of classification and labelling of chemicals).

3. **Labelling must be legible**, for instance in open letter type and font size equivalent to Miriad bold 10.

4. The **official language(s)** in which the intended use is displayed should be relevant to the region in which the RDT product will be used. In the example below, English, French, Spanish and Portuguese are displayed.

5. Display the essential information on the top (see Figure 2), **front and at least one lateral side of the RDT box (left or right)** (see Figure 3). The label contains all the relevant information required for stock management (e.g., product identity, storage conditions and material provided). An exception can be made for custom or variable prints, such as lot number and expiration date, and, in case of use, also production date. These can be printed on only one side of the box.
What should be displayed:

1. **Product name** with sufficient detail for the user to uniquely identify the device and its intended use, e.g.:
   - commercial name of the RDT product
   - “malaria”
   - targeted species and antigen(s)
   - “antigen” or “Ag”

   Example: Commercial name, Malaria Pf/Pv (HRP2/pLDH) Antigen (RDT)

2. **Product code (and symbol)**

3. **Intended use** (to be included if the product name does not include sufficiently specific information). If there is insufficient space on the label, this statement can be included on the IFU: diagnosis of malaria, in vitro diagnostic, single-use

4. **Number of tests** provided in the kit box

5. **In vitro diagnostic** (symbol)

6. Name and physical address of the legal manufacturer

7. Telephone and/or fax number and/or website

8. **Lot number (and symbol)**

9. **Expiration date** (and symbol)
   Preferred format: YYYY-MM

10. **Materials (content) and quantities**
    Materials provided, and quantities of each
    Items required but not provided, i.e. those items required for safe, accurate use of the test, such as a lancet (with symbol)

11. **Storage conditions** (symbols)

12. **Warnings or precautions** (symbols)
    For instance: – do not use if package is damaged (symbol)
    - read instructions before use (symbol)
    - biohazard (symbol)

13. **Additional warning in case the procedure or IFU has changed substantially**
    Clearly visible label, for instance fluorescent orange, and information about the change and effective date should be included in the box as a separate note, or on the IFU.

**Action:** Discuss with country programmes how long they think this warning sticker should remain in place.
### Figure 2.
Required information on the label on the top of the RDT box. Blue indicates specific RDT product items

<table>
<thead>
<tr>
<th>IVD</th>
<th>4 °C</th>
<th>30 °C</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Commercial name, Malaria Antigen Pf/Pan (HRP2/ pLDH) RDT</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>XXXXXXXXXXXX</td>
<td>XX</td>
<td></td>
</tr>
<tr>
<td><strong>Rapid test for the antigen detection of malaria (Plasmodium x)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Test rapide de détection d’antigène du paludisme (Plasmodium x)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Prueba rápida para detección de antígeno de malaria (Plasmodium x)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Teste rápido para detecção de antígeno da malária (Plasmodium x)</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>LOT</th>
</tr>
</thead>
<tbody>
<tr>
<td>XXXXXXX</td>
</tr>
</tbody>
</table>

**Required but not provided**: Gloves, Biosafety sharps container, Biohazard waste container, Timer

### Figure 3.
Proposed labelling of one lateral side and the front of an RDT box. Blue indicates specific RDT product items

<table>
<thead>
<tr>
<th>REF</th>
</tr>
</thead>
<tbody>
<tr>
<td>XXXXXXXXXXXX</td>
</tr>
</tbody>
</table>

| **Content:** |
| XX indicates quantities. Could state number of pouches and what each pouch contains |
| Cassettes (XX) |
| Alcohol swabs (XX) |
| Lancets (XX) |
| Specimen transfer devices (XX) |
| Buffer bottle (XX) |
| Instructions for use (X) |

<table>
<thead>
<tr>
<th><strong>LOT</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>XXXXXXX</td>
</tr>
</tbody>
</table>

**STERILE**

| **Required but not provided:** |
| Gloves |
| Biosafety sharps container |
| Biohazard waste container |
| Timer |

<table>
<thead>
<tr>
<th><strong>4 °C</strong></th>
<th>30 °C</th>
</tr>
</thead>
<tbody>
<tr>
<td>YYYY-MM</td>
<td></td>
</tr>
</tbody>
</table>

**Indicate symbol for method of sterilization**
2. LABELLING OF KIT CONTENTS

General note: According to ISO 18113-2:2009, in the case of a kit, each component shall be identified by name, letter, number, symbol, colour or graphics in the same manner on all labels and in the instructions for use.

Labelling of cassette packaging

What should be displayed:

1. **Product name** with sufficient detail for the user to uniquely identify the product and its intended use, e.g.:
   - commercial name of the RDT product
   - “malaria”
   - targeted species and antigen(s)
   - “antigen” or “Ag”

   Example: Commercial name, Malaria Pf/Pv (HRP2/pLDH) Antigen(RDT)

2. **Product code** *(symbol)*

3. **Intended use** *(to be included if the product name does not include sufficiently specific information):* If there is insufficient space on the label, this statement can be included on the IFU: diagnosis of malaria, in vitro diagnostic, professional use only, point-of-care

4. **In vitro diagnostic** *(symbol)*

5. **Name (or logo) of the legal manufacturer**

6. **Lot number**

   The lot number is preferably identical to the one on the RDT box.

7. **Expiration date**

   Preferred format: YYYY-MM

   The expiration date is preferably identical to that on the RDT box. The expiration date must not be earlier than the expiration date on the RDT box and test packaging.

8. **Quantity of tests per packaging (if more than one test)**

9. **Unless there is no space, list contents of packaging and quantities**, including desiccant

10. **Storage conditions** *(symbols)*

11. **Warnings or precautions** *(symbols)*

    For instance: do not use if package is damaged (symbol)

    read instructions before use (symbol)

    single use (symbol)

Where labels should be put:

Display all standard generic information on one side of the packaging and the custom or variable information (expiration date, lot number) on the opposite side.
**3. LABELLING OF THE CASSETTE**

**Convention of terms used to describe the orientation of the cassette**

Figure 5 shows the most common RDT, a three-band RDT targeting two antigens (*P. falciparum* and pan-*Plasmodium* antigens) in a two-step procedure (add specimen, next add buffer), with a cassette containing individual specimen and buffer wells. The following convention of terms is used: proximal (closest to the specimen and buffer wells) and distal (at the end of the migration [absorption] pad). A vertical view of the cassette in a vertical view (with the direction of the specimen and buffer flow “upwards”) shows a right- and a left-hand side.

**Labelling:**

1. Printing in indelible ink is recommended instead of characters embossed in the cassette housing. The test and control line legends and the actual test lines should be well aligned.

2. All printing should be along the short axis.

3. A single, unequivocal reading legend should be present on the right-hand side of the results window.

4. Abbreviations listed in document “Abbreviations”. In addition, “1” for the sample well, “2” for the buffer well (chronological order)

5. Labelling must be legible: for instance, open letter type, clear print
**Note:** The cassette surface should be of a material (and profile) on which it is possible to write (with a standard ink pen or pencil). Space should be left for writing patient identification.

**What should be displayed:**

1. Product name (with indication of “Malaria”, antigen-based “Ag”, the *Plasmodium* species and the antigens detected) or logical abbreviation (referenced in the IFU)

2. Specimen and buffer wells (see above)

3. Reading legend with *Plasmodium* species detected (see abbreviations: Pf, pan, Pv)

**FIGURE 5.**

Conventions for terms to describe the cassette

4. **LABELLING OF THE BUFFER BOTTLE**

**General requirements and outlines** for labelling RDT buffer bottles:

1. **Labels:** Well-fixed water-resistant label (applied with water-resistant glue) or permanent printing, indelible ink lasting the life span of the RDT product.

2. **Use only internationally recognized symbols** (ISO 15223–2012).
3. The official language(s) displayed should be relevant to the region in which the RDT product will be used.

What should be displayed:

1. **Product name**, with sufficient detail for the user to uniquely identify the product and its intended use, e.g. (preferred option)
   - commercial name of the RDT product
   - “malaria”
   - targeted species and antigen(s)
   - “antigen” or “Ag”

Example: Commercial name, Malaria Pf/Pv (HRP2/pLDH) Antigen(RDT)

or with sufficient detail for the user to identify the type of product with which to use the buffer, e.g. Malaria RDT (acceptable option)

2. **Contents**: Buffer (Bottle)

3. **For product code** (symbol) (preferred option)
   - or a reference code that is also written on the RDT packaging and/or in the instructions for use (acceptable option)

4. **In vitro diagnostic** (symbol)

5. **Name** (or logo) of the legal manufacturer

6. **Lot number** (and symbol)

7. **Volume of contents** or **number of examinations that can be performed**

8. **Expiration date** (symbol)

   Preferred format: YYYY-MM

   The expiration date must not be earlier than the expiration date on the RDT box and test packaging.

9. **Storage conditions** (symbols)

10. **Warnings or precautions** (symbols)

    For instance: do not use if package is damaged (symbol)

    hazard symbol if sodium azide concentration is ≥ 0.1% (symbol)

Where the labels should be put (preferred option)

**FIGURE 6.**
Proposal for printing relevant information on the buffer bottle
5. LABELLING OF ACCESSORIES

Definitions
Accessories of in vitro diagnostics are articles specifically and explicitly intended by the manufacturer to be used with a device to enable that device to be used in accordance with the intended purpose (ISO 18113-1, CE Directive 98/79). Specimen transfer devices, lancets, alcohol swabs and desiccant are included.

General requirements and outlines:
1. **Labels** should be printed on the device or packaging as permanent printing or applied as water-resistant labels (with water-resistant glue). The ink should be indelible and should last the life span of the product. If it is not practicable to display the information on the device itself (e.g. lancets, specimen transfer devices), some or all of the information may appear on the **packaging of multiple items devices (if used)** (GHTF/SG1/N70/2011:5.0 and Annex 1.8.8.1 of EU Directive 98/79).

2. **Use of symbols**, when adequate, is encouraged instead of text. Only internationally recognized symbols (ISO 15223-2012) should be used.

3. The **language(s)** used should be relevant to the region in which the RDT product will be used.

4. The table below lists the **information** to be displayed on different accessories or on their packaging.

<table>
<thead>
<tr>
<th>LABEL INFORMATION</th>
<th>TRANSFER DEVICE</th>
<th>LANCET</th>
<th>ALCOHOL SWAB</th>
<th>DESICCANT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name of accessory</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Intended use if name of accessory does not indicate it</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>(sufficient to identify the device and its intended use: e.g. transfer device, antiseptic, desiccant)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Name of the legal manufacturer of the accessory (preferred to RDT manufacturer)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>For alcohol swab: antiseptic, product and concentration (e.g. isopropyl alcohol70%)</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Product code of the accessory</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>LABEL INFORMATION</strong></td>
<td><strong>TRANSFER DEVICE</strong></td>
<td><strong>LANCET</strong></td>
<td><strong>ALCOHOL SWAB</strong></td>
<td><strong>DESICCANT</strong></td>
</tr>
<tr>
<td>--------------------------------------------------------------------------------------</td>
<td>---------------------</td>
<td>------------</td>
<td>------------------</td>
<td>--------------</td>
</tr>
<tr>
<td>For a transfer device other than inverted cup and loop:</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>permanent</strong> volume mark</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lot number</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Indicate “in vitro diagnostic” use</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Expiration date (<strong>preferred format</strong>: YYYY-MM)</td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td><strong>Quantity of items, indicated on the outer packaging (if applicable)</strong></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Specimen volume transferred</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single use (<strong>symbol</strong>)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Sterile (<strong>and by what method</strong>), if applicable*</td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Do not use if package is damaged (<strong>symbol</strong>)</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td><strong>Warning</strong>: “Do not swallow or eat” and “harmful” (<strong>text or symbols</strong> <strong>) in relevant language(s)</strong></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Interpretation of colour change, if applicable</td>
<td></td>
<td></td>
<td></td>
<td>(X)</td>
</tr>
</tbody>
</table>
## ANNEX 1. AGENDA

<table>
<thead>
<tr>
<th>26 FEBRUARY 2015</th>
<th>CHAIR: J. JACOBS</th>
</tr>
</thead>
<tbody>
<tr>
<td>09:00–09:15</td>
<td>Introduction, review of meeting objectives &amp; agenda</td>
</tr>
<tr>
<td>09:15–09:45</td>
<td>Opportunities for harmonization: Roll Back Malaria experience</td>
</tr>
<tr>
<td>09:45–10:00</td>
<td>Questions and answers</td>
</tr>
<tr>
<td>10:00–10:15</td>
<td>Overview of WHO product testing and current procurement recommendations</td>
</tr>
<tr>
<td>10:15–10:30</td>
<td>Overview of WHO prequalification of diagnostics and malaria RDT pipeline</td>
</tr>
<tr>
<td>10:30–10:45</td>
<td>Coffee break</td>
</tr>
<tr>
<td></td>
<td><strong>Review of recommendations and timetable for implementation: terms, labelling and instructions for use</strong></td>
</tr>
</tbody>
</table>
| 10:45–11:15      | Terms and abbreviations  
|                  | • Required or desirable  
|                  | • Timetable for compliance | Moderator: J. Cunningham |
| 11:15–12:00      | Labelling of the box and cassette packaging  
|                  | • Required or desirable  
|                  | • Timetable for compliance | Moderator: R. Meurant |
| 12:00–12:30      | Labelling the cassette  
|                  | • Required or desirable  
|                  | • Timetable for compliance | Moderator: T. Visser |
| 12:30–13:30      | Lunch |
| 13:30–14:00      | Labelling the cassette (continued)  
|                  | • Required or desirable  
|                  | • Timetable for compliance | Moderator: T. Visser |
| 14:00–14:45      | Labelling the buffer and accessories  
|                  | • Required or desirable  
|                  | • Timetable for compliance | Moderator: J. Jacobs |
| 14:45–15:30      | Instructions for use  
|                  | • Required or desirable  
|                  | • Timetable for compliance | Moderator: R. Meurant |
| 15:30–15:45      | Coffee break |
| 15:45–16:15      | Harmonization of RDT procedural characteristics  
<p>|                  | • Technical requirements and implications for procurement, registration and prequalification | Y.S. Hong |
| 16:15–16:30      | Discussion |
| 16:30–16:50      | Overview of current alignment and misalignment of RDT procedures and labelling practices | T. Visser |
| 16:50–17:10      | Discussion |
| 17:10–17:30      | Alternatives to facilitate procurement and reduce errors and retraining needs | J. Cunningham |
| 17:30–17:45      | Discussion | All |</p>
<table>
<thead>
<tr>
<th>27 FEBRUARY 2015</th>
<th>CHAIR: L. BARAT</th>
</tr>
</thead>
<tbody>
<tr>
<td>8:30–9:15</td>
<td>Summary of day 1 conclusions, questions and answers</td>
</tr>
<tr>
<td>9:15–9:35</td>
<td>Proposed updated WHO procurement criteria</td>
</tr>
<tr>
<td>9:35–10:00</td>
<td>Discussion</td>
</tr>
<tr>
<td>10:00–10:30</td>
<td>Outstanding issues</td>
</tr>
<tr>
<td></td>
<td>• Single packs: buffer vials, IFU, self-testing</td>
</tr>
<tr>
<td></td>
<td>• Lancets</td>
</tr>
<tr>
<td>10:30–10:45</td>
<td>Coffee break</td>
</tr>
<tr>
<td>10:45–11:30</td>
<td>Outstanding issues (continued)</td>
</tr>
<tr>
<td></td>
<td>• Specimen transfer devices</td>
</tr>
<tr>
<td></td>
<td>• Additional supplies</td>
</tr>
<tr>
<td></td>
<td>• Desiccants</td>
</tr>
<tr>
<td>11:30–12:30</td>
<td>Uptake and monitoring of compliance</td>
</tr>
<tr>
<td></td>
<td>• WHO product testing: checklist (S. Incardona)</td>
</tr>
<tr>
<td></td>
<td>• WHO prequalification: dossier (H. Ardura-Garcia)</td>
</tr>
<tr>
<td></td>
<td>• Procurers (panel)</td>
</tr>
<tr>
<td></td>
<td>• Regulators (panel)</td>
</tr>
<tr>
<td>12:30–14:00</td>
<td>Lunch</td>
</tr>
<tr>
<td>14:00–14:30</td>
<td>Next steps and action plan</td>
</tr>
<tr>
<td>14:30–15:00</td>
<td>Conclusions and any other business</td>
</tr>
</tbody>
</table>
ANNEX 2. LIST OF PARTICIPANTS

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ANNEX 3. MEETING PRESENTATIONS

ANNEX 3.1 150226 WHO GMP Meeting Harmonization RDTs.pdf
ANNEX 3.2 GMP-RDT Harmonization - JC-1-FINAL.pdf
ANNEX 3.3 15 02 26 Ardura WHO PQDx overview and malaria pipeline.pdf
ANNEX 3.4 WHO HarT Geneva Feb 2015.pdf
ANNEX 3.5 RDT harmo meeting_RDT similarities_final.pdf
ANNEX 3.6 GMP-RDT Harmonization - JC-2-FINAL.pdf
ANNEX 3.7 GMP-RDT Harmonization - Summary Day 1 & Procuremnt Criteria.pdf
ANNEX 3.8 RDT harmo meetg_Product testing checklist_25feb15.pdf
ANNEX 4. BACKGROUND READING: OUTSTANDING ISSUES IN HARMONIZATION

Background

After the Roll Back Malaria–Institute of Tropical Medicine, Antwerp, stakeholder consultation on enhanced harmonization of malaria rapid diagnostic tests (3–5 December 2013), a harmonization task force was established to discuss and investigate opportunities for harmonization on topics for which consensus was not reached and to consider in more detail the cost implications of any changes that would be required of manufacturers to align with the recommendations.

No consensus on requirements was reached for the following topics:

1. Labelling and IFU requirements for RDT single packs
2. Preferred specifications for lancets
3. Preferred specimen transfer device
4. Supplemental accessories to be included in RDT boxes
5. Preferred specifications for desiccant

1. LABELLING AND IFU REQUIREMENTS FOR RDT SINGLE PACKS

In the past 2 years, malaria RDTs have been increasingly available in single packs comprising the RDT, single-use buffer vial, accessories (alcohol swab, specimen transfer device, lancet) and IFU. The demand appears to be associated with the lower price of this product and extension of RDT use by lower-level providers and community health workers, who see fewer patients, in areas where malaria prevalence is decreasing, in the private sector and probable self-testing by patients and travellers.

Issues impeding consensus

- There is no foreseeable reason why labelling and IFU requirements should be different for single packs; however, physical size limitations are restrictive, and the requirements must therefore be modified.
- Currently, single packs are sold not as single units but as multiple units packaged in a single box; they are, however, distributed or sold as individual units.

Some provisions for “self-testing” in Directive 98/79/EC on in vitro diagnostics and in GHTF/SIG1/N70:2011 are outlined below. They may be applicable even though they are not intended for malaria RDT single packs for “self-testing” purposes.

- The information and instructions provided by the manufacturer should be easily understood and applied by the user.
- Devices for self-testing must, where reasonably possible, include user control, i.e. a procedure by which the user can verify that, at the time of use, the product will perform as intended.
The results should be expressed and presented in a way that is readily understood by a lay person; information should be provided with advice to the user on action to be taken in the case of a positive, negative or indeterminate result and on the possibility of a false positive or a false negative result.

Some particulars may be omitted, provided that the other information supplied by the manufacturer is sufficient to enable the user to use the device and to understand the result(s) produced.

The information provided must include a statement clearly stating that the user should not take any decision of medical relevance without first consulting his or her medical practitioner.

The information must also specify that, when the device is used for self-testing to monitor existing disease, patients should adapt their treatment only if they have the appropriate training to do so.

The IFU and the label must include a translation into the appropriate language(s).

### 2. PREFERRED SPECIFICATIONS FOR LANCETS

A wide range of lancets are available on the market: plain metal lancets and safety-seal lancets are the most common. Published studies, comments from implementers and field observations suggest that auto-lancing or auto-retractable lancets may be preferable as they reduce discomfort, reduce the risk of contamination and reduce risk in rare cases of mishandling (re-use; inappropriate disposal).

**Issues impeding consensus**

- Additional research is required to make the case for one type of lancet or another.
- Cost–effectiveness of auto-retractable lancets

### 3. PREFERRED SPECIMEN TRANSFER DEVICE

RDTs may contain a range of specimen transfer devices, including loops, (glass) capillary tubes, straw pipettes, pipettes and inverted cups. These may or may not be calibrated or have a volume mark indicated.

Few comparative assessments of performance or ease of use have been conducted; however, some data support a preference for the inverted cup. Hopkins et al. enrolled 227 health workers in three countries and assessed the accuracy, safety and ease of use of five devices based on finger-prick whole blood collection. The inverted cup device gave the best overall
performance and was considered the most appropriate choice for use with RDTs by the majority of participating health workers. The loop also performed well, with similar accuracy and precision of blood volumes transferred but slightly lower scores for other characteristics.

There was general agreement not to use glass capillaries (biosafety, CLSI H04-A6; CDC 2008) or tiny (difficult to manipulate) devices such as some types of straws.

**Issues impeding consensus**
- Additional studies are needed to make a definitive recommendation: other specimen types and cadres of health workers?
- Recommend inverted cup or loop, which has similar accuracy and health worker preference; but loops are less safe because of frequent (38%) repeat attempts to collect blood.
- Can one device meet all variable volume requirements?
- Are “preferable” transfer devices compatible with all sample well designs?
- Does the inverted cup perform equally well when used to transfer blood from a tube or from a finger-prick blood drop?

**4. SUPPLEMENTARY BUFFER AND ACCESSORIES TO BE INCLUDED IN RDT BOXES**

In the field, buffer bottles are lost or there are shortages before all RDTs have been performed; this can lead to the bad practice of buffer substitution, which in turn can result in erroneous RDT results. This problem could be mitigated by the inclusion of one (or more) bottles of buffer in each RDT box and/or additional buffer.

Similarly, accessories may be broken or contaminated by accident, with no alternative replacement. Therefore, the number of items should be in excess of the number of RDT cassettes.

From the manufacturers’ perspective, this is not typical practice but could be accommodated.

**Issues impeding consensus**
- No consensus could be reached on the number or percentage of additional buffer or accessories to be provided.
- How does this apply to RDT single packs?
- Preliminary survey data suggest that the cost of an additional bottle of buffer would be US$ 1–1.25 or US$ 0.05 per test.
- Additional alcohol swabs, specimen transfer devices and lancets would cost about US$ 0.05 per test.
- Additional freight costs should also be considered.

**5. PREFERRED SPECIFICATIONS FOR DESICCANT**

A major constraint of RDTs is degradation by extreme temperatures and humidity. Therefore, strict temperature control and protection against humidity during transport and storage is necessary. Protection from humidity is assured by packing
each individual RDT device (cassette or strip) in a sealed, impermeable pouch containing a desiccant, which absorbs humidity. Desiccants for in-vitro diagnostic products may include silica gel, a molecular sieve or Montmorillonite clay. Silica gel may be coated with a humidity-sensitive indicator, which changes its colour to indicate when the maximal absorption capacity has been reached and the silica gel is saturated. In industry, silica gel with humidity indicator is referred to as “self-indicating”, in contrast to non-indicating gel. They are “partial-indicating” if only a portion of the beads are coated. Cobalt dichloride, the most commonly used humidity indicator, should be avoided, as it is carcinogenic. Methyl violet and iron salts are alternatives.

Barbé et al.14 assessed the desiccants in 50 commercially available RDT kits and found that > 40% were not self-indicating, and 4.6% of the products containing self-indicating desiccant showed saturation.

Cost is the probable reason for use of non-indicating desiccants: the estimated wholesale price of a sachet of self-indicating silica gel is US$ 0.70–0.95 while that of a sachet of partial-indicating gel is US$ 0.50–0.70 (Byung-Ki Cho, personal communication, 27 March 2012).

Currently, the WHO procurement guidance21 is “... preference should be given to desiccants with a colour indicator of humidity. It is the responsibility of the manufacturer to provide accurate information on the properties, safety hazards, remedies and safe disposal of any such desiccants.” Elsewhere in the document, however, it is stated: “The absence of desiccant from a manufacturer’s specification and product is not a deficiency, as specific RDTs may not require a desiccant.”

Desiccants. From reference 18

Issues impeding consensus

- Are desiccants an absolute requirement? If not, when can they be excluded?
- Is the evidence sufficient to prefer self-indicating to partial-indicating desiccants?
LIST OF ACRONYMS

GMP Global Malaria Programme
IFU instructions for use
ISO International Organization for Standardization
PQDx programme for prequalification of in vitro diagnostics
RDT rapid diagnostic test
UNICEF United Nations Children’s Fund

ENDNOTES

1. “Implementers” introduce RDTs into programmatic settings.
3. http://www.malariajournal.com/content/13/1/505, additional files: http://www.malariajournal.com/content/13/1/505/additional
5. This applies only to multipack RDT kits and not single packs, which were discussed under “outstanding issues”.
7. http://www.malariajournal.com/content/13/1/505
10. Recommendations received from participants by the time of publication of the report include the following:
   • Guidance is needed on discarding cassettes and venous blood (if used).
   • A humidity range could be specified, as is done for temperature.
   • Give an example of an appropriate disinfectant for cleaning up spills.
15. In the case of malaria RDTs, the control line becomes visible if sufficient dye-labelled antibody (carried in the buffer) accumulates on the test strip line containing sufficient, intact bound capture antibody.
16. Antigens are not recombinant.

