Global **Malaria** Programme

Harmonization of rapid diagnostic tests for malaria and implications for procurement

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Meeting report

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Table of contents

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"[1] and regulatory experts, in December 2013,[2] and subsequently amended, refined and recently published by a "harmonization task force".[3] To complement the review, additional analyses were conducted to determine variation and similarities in the procedural characteristics[4] 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;[5]
- 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.[6] 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*.[7]

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[8] (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 publically 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,[9] 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