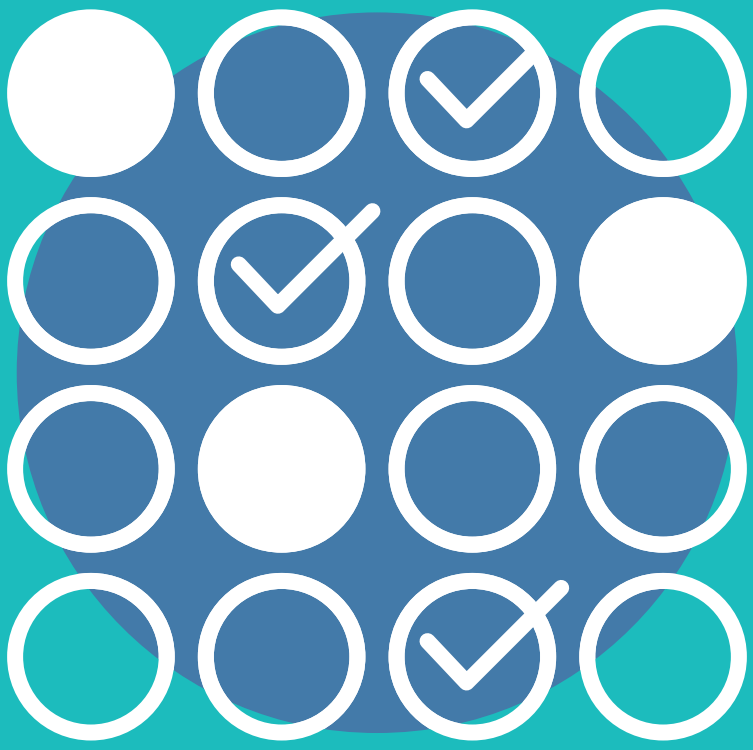
Tests for glucose-6-phosphate dehydrogenase activity

Target product profiles



World Health Organization

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Tests for glucose-6-phosphate dehydrogenase activity: target product profiles

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CONTENTS

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LIST OF ABBREVIATIONS

G6PD	glucose-6-phosphate dehydrogenase
Hb	haemoglobin
PPC	preferred product characteristic
TPP	target product profile
WHO	World Health Organization

OVERVIEW

The *Global technical strategy for malaria 2016–2030 (1)* aims at harnessing and expanding research to accelerate progress towards the elimination of malaria. It encourages innovation and the development of new tools and strategies to maintain progress in malaria control and advance towards elimination. To accelerate implementation of the strategy, in 2018, the World Health Organization (WHO) Global Malaria Programme reviewed its policy-making process to ensure that it is transparent, consistent, efficient and predictable. One of the outcomes of the review was the adoption of "preferred product characteristics" (PPCs) or "target product profiles" (TPPs) as key tools to incentivize and guide the development of urgently needed health products. The use of PPCs and TPPs is aligned with an organization-wide effort to improve communication about public health needs and to facilitate innovation to meet those needs. WHO PPCs and TPPs seek to communicate unmet public health needs; to stimulate the development of relevant new products to meet those needs; and to facilitate the timely, effective assessment of new products, and the formulation of policy recommendations and prequalification listings. Within the Global Malaria Programme, the Diagnostics, Medicines and Resistance Unit is developing a series of PPCs and TPPs to encourage further innovation in diagnostics and medicines. The TPPs published here describe the characteristics of new types of diagnostics to measure glucose-6-phosphate dehydrogenase (G6PD) activity. These diagnostics are expected to facilitate safe and effective treatment with 8-aminoquinolines to prevent *Plasmodium vivax* relapse and reduce onward malaria transmission. They may also have other applications, such as screening neonates for G6PD deficiency, investigating acute haemolytic anaemia and genetic counselling.

The target audience consists of all those working to evaluate assays or to develop new assays for G6PD testing. This document is relevant to those groups who wish to obtain WHO policy recommendations for use and WHO prequalification for their products. All the requirements contained in WHO guidelines for WHO policy recommendation and prequalification will also apply *(2)*. The TPP criteria, developed by an expert stakeholder group over a series of consultations, outline some of the considerations that will be relevant in WHO's case-by-case assessments of G6PD assays in the future. Therefore, should an assay's profile be sufficiently superior to the acceptable characteristics under one or more categories, this may outweigh failure to meet another specific critical characteristic. Assays that fail to meet multiple critical characteristics are unlikely to achieve favourable outcomes in WHO's processes. Likewise, desirable characteristics should not be considered the maximum desirable characteristics; assays that exceed these characteristics may be found favourable during WHO's review processes.

TERMINOLOGY

PPCs are designed to communicate unmet public health needs identified by WHO, stimulate innovation and investment in the identified areas, and communicate the desired performance and operational characteristics of health products to address those needs. The target audience consists of product developers, including researchers, regulatory agencies, procurement agencies, and funders of research and development. PPCs are usually developed before a mature pipeline of products is available and should reflect the ideal characteristics of interventions required to rapidly and effectively achieve global health impact.

TPPs in the context of public health are used to set research and development targets for manufacturers and researchers to guide the development of specific products. TPPs provide more detailed information than PPCs and include both minimally acceptable and preferred performance characteristics.

1. BACKGROUND

G6PD deficiency is the most common enzyme deficiency in the world, affecting approximately 400 million people. It is an X-linked recessive disorder. G6PD is found in the cytoplasm of all cells in the body and plays a vital role in the prevention of cellular damage from reactive oxygen species. It does this by providing substrates to prevent oxidative damage. Red blood cells are particularly vulnerable to reactive oxygen species due to their role in oxygen transport and the inability to replace cellular proteins as mature cells, and they are dependent on G6PD-mediated metabolism to counter oxidative stress. While most people are unaware of having G6PD deficiency and go through life without suffering ill effects, certain drugs, such as 8-aminoquinolines, cause oxidative stress that can result in acute haemolysis of red blood cells. The use of primaquine, an 8-aminoquinoline, for radical cure of *P. vivax* is a major risk factor for haemolysis in groups with G6PD-deficient phenotypes common in malaria-endemic areas. To this end, WHO advises that an individual's G6PD status be used to guide the dose and duration of primaquine therapy. Recently, a new long-acting 8-aminoquinoline, tafenoquine, has been registered. This drug is contraindicated in individuals with less than 70% of normal G6PD activity, effectively mandating quantitative G6PD testing to guide drug administration. In addition, to support the needs of the malaria community, there are also unmet needs for G6PD testing to screen neonates to reduce the immediate risks of hyperbilirubinaemia and kernicterus, and to avert future risk of haemolytic events through early diagnosis.

The reference standard for determining G6PD activity is considered to be the measurement of nicotinamide adenine dinucleotide phosphate production by ultraviolet-visible spectrophotometry at a wavelength of 340 nm over a predefined time interval at standardized temperatures. Separate determination of haemoglobin (Hb) concentration is required. Access to spectrophotometric determination of G6PD activity is limited in most low- and middle-income countries where G6PD is prevalent because this technique is laboratory-based and requires significant expertise. Fortunately, point-of-care G6PD testing solutions have been commercialized in recent years and offer the potential to maximize the benefits of *P. vivax* radical cure, while minimizing the risk. Importantly, these types of tests have different characteristics in terms of their technical capacity to report G6PD activity, their complexity and their price. In order to assess the suitability of currently available products and to shape ongoing and future development of G6PD tests, WHO is coordinating the development of TPPs for G6PD tests to clearly lay out the parameters that will best meet public health needs for *P. vivax* control. Parameters may need to be adjusted to meet other G6PD testing needs, in particular related to the detection of critical thresholds of activity.

The development of phenotypic tests for G6PD is subject to particular challenges due to many sources of variability: between variants, in different populations and age groups, between "reference" laboratory assays, between laboratories and even within laboratories running the same assays *(3)*. There are no international standard materials or universal thresholds that neatly define G6PD deficiency, intermediate or partial G6PD deficiency, and normal G6PD status in both sexes. Convergence around a very limited set of commercial quantitative reference assays and the availability of well characterized, cryopreserved samples with known G6PD activity will be required to support product development and consistently and accurately determine if the proposed performance requirements are being met.

The two TPPs outlined here are **not companion diagnostics for primaquine or tafenoquine**. The G6PD activity measured by the test is a tool to inform risk assessment, guide diagnosis and facilitate clinical decision-making; however, it is not the test itself that determines whether a subsequent action taken by a health care provider is safe or unsafe, appropriate or inappropriate. Both proposed products are intended to determine G6PD activity.

For **the G6PD triage or screening test (TPP #1)**, testing is at the point of care when there is an acute need to determine G6PD activity, which may be expressed through visual indicators corresponding to specific thresholds or as point (numerical) estimates. The test may or may not be dependent on external devices. The specific thresholds of interest proposed are 30% and 70% of normal G6PD activity.
The 30% threshold is informed by the discriminatory power of screening tests that have been the standard of practice for decades and reviews of male G6PD-deficient phenotypes *(4)*. The 70% threshold is the required discriminatory power of a test to assist in decision-making for tafenoquine *(5)*. Neither threshold is intended to assign a definition of "normal" G6PD activity. **One must consider the target population and the testing objective when using a test that can only discriminate accurately between more than and less than 30% of normal G6PD activity. Such a test cannot discriminate between females who are homozygous for normal G6PD and heterozygous females, who have a range of G6PD-deficient red cells and who are at risk of acute haemolytic anaemia upon exposure to certain medications, such as 8-aminoquinolines.** For TPP #1, confirmatory testing of abnormal results (with the traditional reference standard or TPP #2) will most likely be required in baseline/healthy state to assign life-long G6PD status.

The **one-time quantitative assay for G6PD activity (TPP #2)** is principally intended to establish baseline G6PD activity (phenotype) +/- genotype (of common variants) and Hb concentration, and has the capacity for individual-specific data recall. Although anticipated to be technically more complex then TPP #1 and dependent on some basic laboratory infrastructure, this type of assay will be more accessible than the current reference standard testing, and performance requirements are highly comparable, allowing for one-time testing.

2. METHODS

The TPPs for tests for G6PD activity were developed in accordance with the *WHO target product profiles, preferred product characteristics, and target regimen profiles: standard procedures* (unpublished document, available on request from the WHO Research for Health Department, 2022). Declarations of any competing interests (DOIs) were received from all invited experts. WHO processes were used to assess the declared interests and manage any conflicts of interest. Six members who were invited to participate in the TPP Development Group declared potential competing interests, including grants for research related to G6PD testing, G6PD-related clinical work, receipt of donated G6PD tests, consultancies to diagnostic manufacturers but not involving G6PD tests, consultancies related to G6PD point-of-care test development and evaluation, and travel cost sponsorship by a pharmaceutical company to attend United States Food and Drug Administration (FDA) advisory group meetings. After review and due diligence by the WHO Secretariat, five out of the six candidates' interests were deemed to be not relevant, specific or financially significant; the candidate with a paid consultancy from a company developing a point-of-care G6PD test was deemed to have a relevant, specific and financially significant interest and was, therefore, asked to participate only as an observer.

Five virtual consultations with the TPP Development Group (Annex 1) were held between February and April 2022 to reach consensus on the draft TPPs. This final version was produced following a public consultation in June 2022. No DOIs were obtained as part of the public consultation. TPP documents are dynamic and will be updated as new information indicates the need to make changes to the parameters and characteristics and/or to the identified public health need itself.

3. TPP #1 – POINT-OF-CARE SCREENING OR TRIAGE TEST FOR G6PD ACTIVITY

Characteristic	Acceptable	Desirable	Notes
Target population	All individuals at the time of presentation at the point of care		Groups of special interest include individuals with confirmed *P. vivax* or *P. ovale*, and neonates. The prevalence of G6PD deficiency (in males) in the population may range from 1% to 30%.
Intended use case	To determine in vitro G6PD activity in individuals (male and female)		Indications for testing would be to guide the management of *P. vivax* (+/- *P. ovale*) therapy with 8-aminoquinoline drugs; to guide administration of rasburicase; and to screen neonates for G6PD deficiency.
Target use setting	Level 1	Level 0	See Annex 2. Definition of health system infrastructure levels.
End user	Health care workers or laboratory technicians (see note) with appropriate training in sample collection, biosafety and the use of the test	Same + community health care workers	Community health workers would also be considered acceptable for tests that meet acceptable positive percent agreement/negative percent agreement requirements and have visual or automated read-outs that do not require multi-step interpretation.
Performance			
Analyte	Whole blood G6PD activity	Same + standalone Hb concentration	Whole blood may slightly overestimate G6PD activity compared to red blood cells alone due to G6PD activity in white blood cells. Therefore, white blood cells should ideally be removed, especially if the count is above the upper limit of the laboratory's reference interval. However, this is expected to add requirements for additional processing (complexity), so red blood cell G6PD activity is not required.
Limit of quantification	G6PD ≤ 1.2 U/g Hb	≤ 0.4 U/g Hb for a specimen of 12 g/dL Hb (equivalent to commonly used commercial reference methods)	Limit of quantification is the smallest concentration of analyte in a test sample that can be determined with acceptable repeatability and accuracy; the enzyme activity of specimens in the testing panel should be calibrated against a suitable biological reference material and appropriate reference method.

Characteristic	Acceptable	Desirable	Notes
Performance (cont.)			
Sample types	Finger- (+ heel-) prick (capillary) blood sample and venous whole blood	Same + cord blood	
Percent positive agreement/ percent negative agreement – for qualitative or semiquantitative tests	> or < ~30% of normal G6PD U/g Hb percent positive agreement: ≥ 95%; percent negative agreement: ≥ 90%	Same + ≥ 30% to < 70% and ≥ 70% of normal G6PD U/g Hb percent positive agreement: ≥ 85%; percent negative agreement: ≥ 90%	Test developers must carefully consider the target population and the users' testing objective when considering development of a test that can only discriminate accurately between less than and greater than around 30% activity. Such a test cannot discriminate between females who are homozygous for normal G6PD and heterozygous females, who have a range of G6PD-deficient red cells and who are at risk of acute haemolytic anaemia upon exposure to certain medications such as 8-aminoquinolines. Such a test is essentially limited to characterizing patients with low G6PD enzyme activity, i.e. hemizygous deficient males, homozygous deficient females and some heterozygous females. Proposed "desirable" targets are based on critical thresholds for informing the use of primaquine and tafenoquine that discriminate "deficient" (< 30% activity), "intermediate", which will capture mainly heterozygous females with 30–70% G6PD activity, and "normal" activity (≥ 70% of normal G6PD U/g Hb) for most common variants. If test developers envision that the test could inform the use of tafenoquine, then the desirable criteria should be met or exceeded. The variability in G6PD activity between assays, between laboratories and within laboratories using the same spectrophotometric assays and control samples is well established in Pfeffer et al. *(3)*. Even in the absence of universal thresholds to define G6PD deficiency, WHO will not endorse a single commercial test/brand as the reference standard or reference population set of samples, but WHO prequalification protocols for conducting the laboratory-based evaluation component of prequalification will be publicly available. Alignment with these protocols is advisable to optimize comparability.

Characteristic	Acceptable	Desirable	Notes
Performance (cont.)			
Agreement for quantitative test only	Systematic difference (bias): absolute difference: ± 2 IU/g Hb; fold difference: 0.8–1.2 fold Limits of agreement: absolute difference: ± 2 IU/g Hb; fold difference: 0.8–1.2 fold		Criteria are based on the expectation that the absolute difference between the index test and reference standard cannot be less than the difference produced by repeat testing of the same sample against the reference standard. Criteria are proposed based on spectrophotometry repeatability coefficients generated using data in Pfeffer et al. *(3)*. Differences proposed will not, even in the worst case scenario, lead to classification of deficient as normal or normal as deficient.
Type of analysis	Qualitative to specific threshold of activity: > or < ~30% of normal G6PD U/g Hb	Semi-quantitative (> 1 threshold) or quantitative	Relevant qualitative and semiquantitative thresholds may vary depending on the intended use for testing. To support clinical decision-making for malaria case management, thresholds of 30% and 70% of normal activity are most relevant, as they have historically guided the administration of primaquine and, more recently, tafenoquine, respectively.
Interpretation	Distinct visual signals at critical thresholds (colour change) read manually or with some form of operator assistance, e.g. standard colour chart, app or other external optical device	Numerical output in U/g Hb and ideally estimated percent of normal G6PD activity Proprietary instrument or smart phone application – no calculations required	Expression of U/g Hb and estimated percent of normal G6PD activity could facilitate risk assessment.

Characteristic	Acceptable	Desirable	Notes
Performance (cont.)			
Test procedure	Sample preparation steps: one Reagent reconstitution: easy to do Need to transfer precise volume: autofill or graduated volume markings on sample transfer device provided Time steps: three or less Invalid rate: < 3% invalid results with correct use by operator	Sample preparation steps: none Reagent reconstitution: ready to use Need to transfer precise volume: no, or limited to number of drops Time steps: one, with the potential for digitally guided workflows and built-in timers to reduce user error on timed steps Invalid rate: < 2% invalid results with correct use by operator	
Sample volume	Autofill device ≤ 30 µL	Autofill or direct to device ≤ 10 µL	
Time to results and stability of end-point	Time to result: ≤ 30 minutes Result validity: fixed reading time	≤ 15-minute and 60-minute visual end-point if applicable – stored image or results	
Operating conditions	20–35 °C; 25–90% relative humidity	18–40 °C; 25–90% relative humidity	
Stability of the kit once opened	≥ 30 minutes	≥ 1 hour	This might need to be reduced if ambient temperatures are high, e.g. > 25–30 °C
Training needs	One day with instructions for use and quick reference guide(s)	Less than half a day and option for smart phone application(s) to ensure ongoing compliance and up-to-date training	

Characteristic	Acceptable	Desirable	Notes
Performance (cont.)			
Stability of kit	18 months at 4–35 °C; humidity 75% + 5%; tolerates brief periods > 40°C; any associated equipment must meet or exceed these requirements.	24 months at 4–40 °C; humidity 85% + 5%; tolerates freezing and brief periods > 45 °C; any associated equipment must meet or exceed these requirements.	
Specimen capacity and throughput	Single use (manual or device-based); ≥ 2 samples per hour	Device has capacity for > 1 sample/run @ 15 minutes per run; ≥ 8 per hour	
Quality assurance/quality control	Assurance of correct operation with minimal user-required quality control procedures, e.g. internal control area or region within individual testing device Compatible with positive control and negative control sold separately Calibration control for instruments, if applicable Must have same or more tolerant storage conditions as tests	Same + compatible controls included in the kit; compatible with external quality assessment material	Requirement for separate positive/ negative controls will be a significant impediment to point-of-care use unless they are intrinsic to the test device. If used at the point-of-care level outside of centralized facilities, a formal quality assurance mechanism will likely be required to guarantee product quality at point of use across geographies.
Waste management	Normal laboratory waste stream	Same + biodegradable or recyclable components, e.g. cassette, packaging	

Characteristic	Acceptable	Desirable	Notes
Data management			
Connectivity	Not required for reader-independent tests	If device-based: mobile network, Wi-Fi, USB or Bluetooth; app: mobile network or Wi-Fi as provided by the mobile device	
Language	Not required for reader-independent tests, but all instructions for use should be appropriate for the destination of use and should utilize diagrams to facilitate understanding.	The user shall be able to select preferred language (determined from target markets) from a selection of options, and ideally the device will be easily programmable to incorporate additional languages.	
Memory	Not required for reader-independent tests	≥ 500 patient results (pending upload); ≥ 100 quality control results (pending upload)	
Handling of intermittent connections	Not required for reader-independent tests	The user shall be able to perform tests and receive results offline, in which case the reader shall transmit the data automatically when back online.	
Data exchange standards	Not required for reader-independent tests	The reader supports all of the following formats: Health Level Seven, Fast Healthcare Interoperability Resources and JavaScript Object Notation.	
Data destination	Not required for reader-independent tests	Health programme shall be able to choose the destination of the reader's data – i.e. compatible with standard national health management information systems, country-specific electronic medical records or dedicated G6PD databases.	
Data ownership	Not required for reader-independent tests	In compliance with local authorities and regulations, the health programme shall be able to set the ownership of the reader's data.	

Characteristic	Acceptable	Desirable	Notes
Data management (cont.)			
Data security and privacy	Not required for reader-independent tests	To facilitate use by health programmes in accordance with the laws, regulations and policies of their settings and best practices, the reader shall provide configurable features so that personal data can be: • gathered transparently from users and patients, including consent; • collected and processed only for purposes compatible with the health programme's purposes; • limited to what is relevant and necessary; • collected accurately; • stored in identifiable form no longer than necessary; • secured for integrity and confidentiality, with encryption at rest and in transmission.	
Need for additional supplies or equipment	Portable equipment: handheld or on desktop (< 3 kg); battery or solar power operated; > 8 hours rechargeable battery life	No additional equipment beyond the diagnostic instrument required, e.g. micropipettes, vortex, etc. All supplies required for sample collection and testing procedures packaged with the tests, e.g. lancet, alcohol swabs	As the instrument will not be in continuous use, eight hours of battery life could permit use over longer intervals, e.g. weeks before recharging is needed. The need for additional supplies that are required but not provided should generally be minimized.

Characteristic	Acceptable	Desirable	Notes
Data management (cont.)			
Need for maintenance/ spare parts (if applicable)	Swap out or replace ancillary instrument when needed		
Pricing (ex-works) and warranty	< US$ 5.00; instrument: < US$ 700; lifespan: ≥ 12-month replacement warranty; repair policy: ≥ 5 years	< US$ 2.50; instrument: < US$ 400; lifespan: ≥ 24-month replacement warranty; repair policy: ≥ 7 years	Higher prices for instruments could be acceptable if platforms are multipurpose. Test developers may also want to consider instruments/ devices being free of charge when certain volumes of tests are purchased
Product registration	Regulatory approval in malaria-endemic countries and WHO prequalification		Collaborative review procedures for country assessments should be considered to improve efficiency; interim measures, such as approval by the Global Fund Expert Review Panel for Diagnostics, are encouraged, as is registration with stringent regulatory authorities, which may allow fast-tracking of WHO prequalification.

3. TPP #2 – ONE-TIME QUANTITATIVE TEST FOR G6PD ACTIVITY

Characteristic	Acceptable	Desirable	Notes
Target population	Whole population at baseline, healthy state Unhealthy individuals at the time of presentation, if baseline G6PD status unknown or if original results were at age < 1 year		Primary target populations will be individuals (all genders) living in areas where G6PD deficiency is prevalent, ranging from 1% to 30% in males, and where *P. vivax* and *P. ovale* are endemic.
Intended use case	In vitro determination of G6PD activity (G6PD U/g Hb) normalized for Hb level: healthy and unhealthy individuals; male and female Recall or extrapolation of baseline G6PD activity at future time (see note), e.g. *P. vivax* infection	Same + standalone Hb measurement (g/dL) +/- determination of common variants/genotypes	As G6PD activity is higher in infants, testing in the first months of life may overestimate future G6PD activity, particularly for heterozygous females with partial/intermediate G6PD deficiency. Therefore, re-testing after 1 year of age may be warranted. Genotyping is considered complementary and will require integration of technologies.
Target use setting	Basic laboratory settings (Level 2), including mobile units; referral sites for abnormal G6PD screening or triage test results	All case management settings, including maternity wards (Level 1)	See Annex 2: Definition of health system infrastructure levels.
End user	Trained laboratory technician	Same + trained health care workers	

Characteristic	Acceptable	Desirable	Notes
Performance			
Analyte	Whole blood G6PD activity and Hb concentration	Red blood cell G6PD activity (see note); Hb concentration and DNA sequences for common variants	Whole blood may slightly overestimate G6PD activity compared to red blood cells alone due to G6PD activity in white blood cells. Therefore, white blood cells should ideally be removed, especially if the count is above the upper limit of the laboratory's reference interval. However, this is expected to add requirements for additional processing (complexity), so red blood cell G6PD activity is desirable but not essential; therefore, this characteristic should not be prioritized over ease-of-use, including portability and price. Specifications need to be developed separately for additional analytes e.g. Hb, DNA sequences
Limit of quantification	G6PD < 0.8 U/g Hb	G6PD < 0.4 U/g Hb; for a specimen of 12 g/dL Hb (equivalent to commonly used commercial reference methods)	Limit of quantification is the smallest concentration of analyte in a test sample that can be determined with acceptable repeatability and accuracy; the enzyme activity of specimens in the testing panel should be calibrated against a suitable biological reference material and appropriate reference method.
Sample types	Finger- or heel-prick (capillary) blood sample or anticoagulated venous blood	Same + umbilical cord blood and/or dried blood spot	
Agreement	Systematic difference (bias): • absolute difference: ± 2 IU/g Hb; fold difference: 0.8–1.2 fold Limits of agreement: • absolute difference: ± 2 IU/g Hb; fold difference: 0.8–1.2 fold	Systematic difference (bias): • absolute difference: ± 1 IU/g Hb; fold difference: 0.9–1.1 fold Limits of agreement: • absolute difference: ± 1 IU/g Hb; fold difference: 0.9–1.1 fold	Criteria are based on the expectation that the absolute difference between the index test and reference standard cannot be less than the difference produced by repeat testing of the same sample against the reference standard. Criteria are proposed based on spectrophotometry repeatability coefficients generated using data in Pfeffer et al. *(3)*. The differences proposed will not, even in the worst case scenario, lead to classification of deficient as normal or normal as deficient.

Characteristic	Acceptable	Desirable	Notes
Performance (cont.)			
Type of analysis	Quantitative		
Interpretation	Numerical hardware reader in U/g Hb +/- percent of normal G6PD activity (proprietary device/instrument or smart phone application) – no calculations required		Ideally, it will be possible to set adjusted male median/100% level and thresholds (e.g. 30% adjusted male median, 70% adjusted male median) and have the device show interpretation directly without the need for the operator to use a crosswalk (e.g. "normal", "intermediate").
Test procedure	Sample preparation steps: two Reagent reconstitution: easy to do or ready to use Need to transfer precise volume: acceptable, but ideally not required Time steps: three or less with the potential for digitally guided workflows and built-in timers to reduce user error on timed steps Time to result: ≤ 30 minutes Result validity: stored image or results Invalid rate: < 4% invalid results with correct use by operator	Sample preparation steps: none or one Reagent reconstitution: ready to use Need to transfer precise volume: not required Time steps: two or less with the potential for digitally guided workflows and built-in timers to reduce user error on timed steps Time to result: ≤ 10 minutes Result validity: stored image or results Invalid rate: < 2% invalid results with correct use by operator	

Characteristic	Acceptable	Desirable	Notes
Performance (cont.)			
Sample volume	≤ 50 µL	≤ 10 µL; autofill transfer device or direct to device	
Operating conditions	15–35°C; 25–80% relative humidity	10–40°C; 25–90% relative humidity	
Stability of the kit once opened	≥ 30 minutes for single-use test after opening the pouch	≥ 1 hour for single-use test after opening the pouch	
Training needs	Two days or less with instructions for use and quick reference guide(s) option for smart phone application(s) to ensure ongoing compliance and up-to-date training (and re-training particularly in low-use settings)	One day or less with instructions for use and quick reference guide(s) option for smart phone application(s) to ensure ongoing compliance and up-to-date training (and re-training particularly in low-use settings)	
Stability of kit	≥ 18 months at 4°C; humidity 75% + 5%; tolerates freezing and brief periods > 40–45°C; any associated equipment must meet or exceed these requirements.	≥ 24 months at 4°C or ≥ 18 months at 18–25°C; humidity 80% + 5%; tolerates freezing and brief periods > 45°C; any associated equipment must meet or exceed these requirements.	
Specimen transport conditions	≥ 48 hours at 2–8°C	≥ 72 hours at ambient temperature (~10–35°C)	
Specimen capacity and throughput	≤ 10–30-minute run time; ≥ 2–6 results/hour for single-use test	Random access, batch in ≥ 5; ≤ 10-minute run time; ≥ 30 results/hour	

Characteristic	Acceptable	Desirable	Notes
Performance (cont.)			
Quality assurance/ quality control	Assurance of correct operation with minimal user-required quality control procedures Positive control and negative control sold separately or included in kit Calibration control for instruments	Same + external quality assessment material compatible	
Safety	Universal precautions for a point-of-care/clinical laboratory test No toxic constituents or waste		
Waste management	Normal laboratory waste stream	Same + biodegradable or recyclable components, e.g. cassette, packaging	
Data management/connectivity			
Connectivity	Mobile network, Wi-Fi or USB	Same + Bluetooth	
Language	The user shall be able to select preferred language from a selection of options (must include English).	The device will be easily programmable to incorporate additional languages.	
Memory	≥ 500 patient results (pending upload); ≥ 100 quality control results (pending upload)	≥ 5000 patient results (pending upload); ≥ 500 quality control results (pending upload)	
Handling of intermittent connections	The user shall be able to perform tests and receive results offline, in which case the reader shall transmit the data automatically when back online.	Same + the reader shall transmit automatically (without user action) in the background when back online.	

Characteristic	Acceptable	Desirable	Notes
Data management/connectivity (cont.)			
Data exchange standards	The reader supports at least one of the following formats: Health Level Seven, Fast Healthcare Interoperability Resources or JavaScript Object Notation.	The reader supports all of the following formats: Health Level Seven, Fast Healthcare Interoperability Resources and JavaScript Object Notation.	
Data destination	Saved on device/instrument and/or computer interface	Health programme shall be able to choose the destination of the reader's data – i.e. compatible with standard national health management information systems, country-specific electronic medical records or dedicated G6PD databases.	
Data ownership	In compliance with local authorities and regulations, the health programme shall be able to set the ownership of the reader's data.		
Data security and privacy	To facilitate use by health programmes in accordance with the laws, regulations and policies of their settings and best practices, the reader shall provide configurable features so that personal data can be: • gathered transparently from users and patients, including consent; • collected and processed only for purposes compatible with the health programme's purposes; • limited to what is relevant and necessary; • collected accurately; • stored in identifiable form no longer than necessary; • secured for integrity and confidentiality, with encryption at rest and in transmission.		
Compatibility with unique patient identifiers	Capacity to link test data to unique patient identifiers, if required; patient identifier codes entered manually	Same + patient identifier codes entered by scanning 1D or 2D barcodes	

Characteristic	Acceptable	Desirable	Notes
Data management/connectivity (cont.)			
Contextual data collected	Time and date of test	Location of testing site (if enabled by the health programme) and ambient temperature	
Portability	Desktop; mains power; surge protection	Handheld or portable (< 3 kg); battery or solar power operated; > 8 hours rechargeable battery life	
Need for maintenance/ spare parts	Swap out or replace ancillary device when needed	None	
Pricing (ex-works) and warranty	Test: < US$ 10; instrument: < US$ 2000; lifespan: ≥ 24-month replacement warranty; repair policy: ≥ 7 years	Test: < US$ 5; instrument: < US$ 1000; lifespan: ≥ 24-month replacement warranty; repair policy: ≥ 10 years	Significantly higher price than malaria rapid tests acceptable, as one-off use per person. Higher prices for instruments could be acceptable if platforms are multipurpose beyond G6PD and potentially outside malaria settings. Test developers may also want to consider instruments/devices being free of charge when certain volumes of tests are purchased.
Product registration	Regulatory approval in malaria-endemic countries and in those with high prevalence of G6PD deficiency (≥ 3%), and WHO prequalification		Collaborative review procedures for country assessments should be considered to improve efficiency; interim measures, such as approval by the Global Fund Expert Review Panel for Diagnostics, are encouraged, as is registration with stringent regulatory authorities, which may allow fast-tracking of WHO prequalification.

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ANNEX 2. DEFINITION OF HEALTH SYSTEM INFRASTRUCTURE LEVELS

Table A2.1 outlines the definition of health system infrastructure levels, as described in Ghani et al. *(1)* and the Maputo Declaration *(2)*.

Table A2.1. Definition of health system infrastructure levels

Characteristics	Level 0	Level 1	Level 2	Levels 3 and 4
Description	In the community or home	Lowest level of health care system with a laboratory	First level of referral health care and laboratories	Second and higher levels of referral health care and laboratories
Examples of locations	In homes, health fairs, health posts, clinics with no laboratory, pharmacies	Health centres (Africa), rural health centres (Asia and Latin America)	Hospitals (Africa), urban health clinics (Asia and Latin America), clinical laboratories in the developed world	Hospitals (Latin America and Asia), national clinical/reference laboratories (Africa), surveillance laboratories, research laboratories
Electricity	Not reliably available	Not reliably available	Available, expected to have refrigeration	Available
Clean water	Not reliably available	Not reliably available	Available	Available
Physical laboratory infrastructure and laboratory equipment	No laboratory	Not all facilities have laboratories. If present, minimally equipped (e.g. microscope, centrifuge) or moderately equipped (see level 2 description) laboratories	Moderately equipped laboratories (e.g. additional equipment for basic chemistry and manual immunoassays)	Well-equipped laboratories (e.g. automated and advanced equipment)
Personnel	Community health care workers, nurses, family members, pharmacists, traditional medicine practitioners	Nurses, sometimes physicians, laboratorians with a range of training	Nurses, physicians, moderately and well-trained laboratorians	Nurses, physicians, well- trained laboratorians

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