World Health Organization

Target product profile – Tests for G6PD activity

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Overview

The *Global technical strategy for malaria 2016–2030* (GTS) aims to harness and expand 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 GTS, in 2018, the World Health Organization (WHO) Global Malaria Programme (GMP) 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 a key tool 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 aim 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 GMP, 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 describes the characteristics of new types of diagnostics to measure G6PD activity which are expected to facilitate safe and effective treatment with 8-aminoquinolines to prevent *P. vivax* relapse and reduce onward malaria transmission, as well as having other applications such as screening neonates for G6PD deficiency, investigating acute haemolytic anaemia and genetic counselling.

The TPP development process followed WHO target product profiles, preferred product characteristics, and target regimen profiles: Standard Procedures (V1.02, 3 August 2020). Five virtual consultations with the TPP Development Group (Annex 1) were held between February and April 2022 to reach consensus on the draft TPPs. The target audience are all those working to evaluate assays or to develop new assays for G6PD. 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 *(1)*. The TPP criteria, developed by an expert stakeholder group over a series of consultations, lay out 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 which fail to meet multiple critical characteristics are unlikely to achieve favourable outcomes from WHO's processes. Likewise, desirable characteristics should not be considered as the maximum desirable characteristics; assays that exceed these characteristics may be round favourable during WHO's review processes.

Terminology

Preferred product characteristics (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, regulatory agencies, procurement agencies, and funders of research and development. PPCs accommodate a number of target product profiles (TPPs).

Target product profiles (TPPs) are generally planning tools used by manufacturers to guide the development of specific products. TPPs generally provide much more detailed information than PPCs, such as intended use, target populations, and safety and efficacy-related characteristics. They include both minimally acceptable and preferred performance characteristics. The minimum performance characteristics should be considered a "go/no-go" decision point in the product development process. The preferred product characteristics should reflect the ideal characteristics required to rapidly and effectively achieve a global health impact.

Acknowledgements

WHO gratefully acknowledges the independent experts comprising the TPP Development Group and the supporting role of members of the WHO secretariat, listed in Annex 1.

Background

Deficiency of glucose-6-phosphate dehydrogenase (G6PDd) is the most common enzyme deficiency in the world, affecting approximately 400 million people. It is an X-linked recessive disorder. Glucose-6-phosphate dehydrogenase (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 (ROS). It does this by providing substrates to prevent oxidative damage. Red blood cells are particularly vulnerable to ROS due to their role in oxygen transport and the inability to replace cellular proteins as mature cells. While most people are unaware of having G6PDd and go through life without suffering ill effects, certain drugs, like 8-aminoquinolines, cause oxidative stress which can result in acute haemolysis of red blood cells, which are dependent on G6PD-mediated metabolism to counter oxidant stress. The use of primaquine, an 8-aminoquinoline, for radical cure of 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 dose and duration of primaquine therapy. Recently, a new, long-acting 8-aminoquinoline has been registered, tafenoquine, which is contraindicated in individuals with < 70% of normal G6PD activity, effectively mandating quantitative G6PD testing to guide drug administration. In addition, to supporting the needs of the malaria community, there are also unmet needs for G6PD testing to screen neonates and reduce the immediate risks of hyper bilirubinaemia and kernicterus and avert future risk of haemolytic events through early diagnosis.

The reference standard for determination of G6PD activity is considered to be the measurement of NADPH production by UV spectrophotometry at a wavelength of 340 nm over a predefined time interval at standardized temperatures. Separate determination of haemoglobin concentration is required. Access to spectrometric determination of G6PD activity is limited in most low- and middle-income countries where G6PD is prevalent because it is laboratory based and requires significant

expertise to operate. 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 and minimize the risk but, importantly, they possess 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 product development for G6PD tests, WHO is coordinating the development of target product profiles for G6PD tests that will 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 detection of critical thresholds of activity.

The development of phenotypic tests for G6PD is known to have particular challenges due to many sources of variability: amongst variants, in different populations and age groups, between "reference" lab assays, laboratories and even within laboratories running the same assays *(2)*. There are no international standard materials or universal thresholds that neatly define G6PD deficient, 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 that informs risk assessments, guides diagnoses and clinical decision making but it is not the test itself that determines if a subsequent action taken by a health care provider is safe or unsafe; appropriate/inappropriate. Both proposed products are intended to determine G6PD activity.

For **the G6PD triage or screening test, (TPP1)**, testing is at the point of care when there is an acute need for G6PD activity determination 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: 30% is informed by discriminatory power of screening tests that have been standard of practice for decades and reviews of male G6PD deficient phenotypes *(3,4)* whilst 70% is the required discriminatory power of a test that can assist 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 < and > ~30% of normal G6PD activity. Such a test cannot discriminate between females 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 haemoglobin 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 it will be more accessible than current reference standard testing and performance requirements are highly comparable allowing for one-time testing.

TPP #1 – Point of care screening or triage test for G6PD activity

Characteristic	Acceptable	Desirable	Notes
Target population	All individuals at time of presentation at the point of care		Groups of special interest include confirmed *P. vivax*, *P. ovale*, neonates. Prevalence of G6PDd (in males) in the population may range from 1–30%
Intended use case	To determine in vitro G6PD activity in individuals (male and female)		Indications for testing would be to guide management of *P. vivax* (+/- *P. ovale*) therapy with 8-aminoquinoline drugs; to guide administration of rasburicases; to screen neonates for G6PDd
Target use setting	Level 1	Level 0	Annex 2: Definition of health system infrastructure levels according to Ghani et al. and Maputo Declaration
End user	Health care workers or laboratory technicians (see note) with appropriate training in sample collection, biosafety and in the use of the test	Same + community health care workers	Community health workers would also be considered acceptable for tests that only meet acceptable PPA/NPA requirements and have visual or automated read-outs not requiring multi-step interpretation
Performance			
Analyte	Whole blood G6PD activity	Same + stand-alone haemoglobin concentration	RBC G6PD activity also acceptable but would imply additional processing step/complexity so it is not considered essential
Limit of quantification	G6PD ≤ 1.2 U/g Hb	≤ 0.4 U/g Hb for a specimen of 12g/dL haemoglobin (equivalent to commonly used commercial reference methods)	Limit of quantification is the smallest concentration of analyte in a test sample that we can determine with acceptable repeatability and accuracy; the enzyme activity of specimens in the testing panel should be calibrated against a suitable

Characteristic	Acceptable	Desirable	Notes
			biological reference material and appropriate reference method
Sample types	Finger- (+ heel-) prick (capillary) blood sample	Same + cord blood and venous (EDTA anticoagulated) whole blood	
Percent positive agreement (PPA)/ Percent negative agreement (PNA) – for qualitative or semiquantitative tests	> or < ~30% of normal G6PD U/gHb PPA: ≥ 95; PNA: ≥ 90%	Same + ≥ 30 % - < 70% and ≥ 70% of normal G6PD U/g Hb PPA: ≥ 85% PNA: ≥ 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 < and > ~30% activity. Such a test cannot discriminate between females 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 use of primaquine and tafenoquine that discriminate "deficient" (< 30% activity), "intermediate" that 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 be used to inform use of tafenoquine then the

Characteristic	Acceptable	Desirable	Notes
			desirable criteria must be met or exceeded. Variability in G6PD activity between assays, labs and in labs using the same spectrophometric assays and control samples is well established (Pfeffer et al. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7224463/pdf/pmed.1003084.pdf) Even in the absence of universal thresholds to define G6PDd, WHO will not endorse a single commercial test/brand as the reference standard or reference population set of samples but WHO PQ protocols for conducting the lab-based evaluation component of PQ will be publicly available. Alignment with these protocols is advisable to optimise comparability.
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 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 with data in Pfeffer et al. (PLoS Med. 2020 May 14;17(5):e1003084) 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
Type of analysis	Qualitative to specific threshold of activity – > or < ~30% of normal G6PD U/g Hb	Semi-quantitative (> 1 threshold) or quantitative	
Interpretation	Distinct visual signals at critical thresholds (colour change) or reader-assisted	Numerical value on hardware reader in U/gHb and estimated % of normal G6PD activity (proprietary device or smart phone application) – no calculations required	Expression of U/gHb and estimated % of normal G6PD activity could facilitate risk assessment
Test procedure	• Sample prep steps 1 • Reagents reconstitution ; easy to do • Need to transfer precise volume: autofill or graduated volume markings on sample transfer device is provided • Time steps: < or 3 • Invalid rate: < 3% invalid results with correct use by operator	• Sample prep steps 0 • Reagents reconstitution: ready to use • Need to transfer precise volume: no or limited to number of drops • Time steps: 1 with the potential for digitally guided workflows and built-in timers to reduce user errors on timed steps • Invalid rate: < 2% invalid results with correct use by operator	
Sample volume	Autofill device ≤ 30µL	autofill or direct to device ≤ 10µL	
Time to results and stability of end point	• Time to result: ≤ 30 minutes • Results validity: fixed reading time	≤ 15 minutes and 60 minutes visual endpoint if applicable – stored image or results	
Operating conditions	15–35 °C; 25–90% relative humidity	10–40 °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	1 day with instructions for use and quick reference guide(s)	≤ 0.5 days and option for smart phone application(s) to ensure ongoing compliance and up-to-date training	
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	

Characteristic	Acceptable	Desirable	Notes
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	
QA/QC	• Assurance of correct operation with minimal user-required QC procedure 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; external quality assessment material compatible	Requirement for separate positive/negative controls will be significant impediment to point of care use unless intrinsic to test device. If used at POC level outside of centralized facilities, likely to require formal QA mechanism 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	
Data management			
Connectivity	Not required for reader independent tests	If device-based: mobile network, Wi-Fi, or USB, 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 to 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 QC 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 that data when back online automatically	
Data exchange standards	Not required for reader independent tests	The reader supports all of the following formats: HL7, FHIR, and JSON	

Characteristic	Acceptable	Desirable	Notes
Data destination	Not required for reader independent tests	Health programme shall be able to choose the destination of the reader's data – i.e. compatibility with standard national HMIS data 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	
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: a. gathered transparently to users and patients, including consent; b. collected and processed only for purposes compatible with the health programme's purposes; c. limited to what is relevant and necessary; d. collected accurately; e. stored in identifiable form no longer than necessary; f. secured for integrity and confidentiality, with encryption at rest and in transmission	
Need for additional equipment	Portable: handheld or on desktop (< 3 kg); battery or solar power operated; > 8 hours rechargeable battery life	No additional equipment beyond the diagnostic device required e.g. micropipettes, vortex, etc.	As device will not be in continuous use, 8 hours of battery life could permit use over longer intervals e.g. weeks before recharging needed

Characteristic	Acceptable	Desirable	Notes
Need for maintenance/ spare parts	Swap out or replace ancillary device when needed	None (device free)	
Pricing and warranty	< US$ 5.00; instrument – < US$ 700; lifespan – ≥ 24-month replacement warranty and repair policy ≥ 7 years	<US$ 2.50; instrument < US$ 400; lifespan – ≥ 24-month replacement warranty and repair policy ≥ 10 years	Higher prices for instruments could be acceptable if platforms are multipurpose. Test developers would also want to consider instruments/devices being free of charge when certain volumes of tests are purchased
Product registration	Malaria endemic countries regulatory approval and WHO prequalification		Collaborative review procedures for country assessments to be considered to improve efficiency; interim measures such as The Global Fund Expert Review Panel for Diagnostics (ERPD) approval are encouraged as is registration with stringent regulatory authorities which may allow fast tracking of WHO prequalification

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 G6PDd is prevalent ranging from 1–30% 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 haemoglobin level – healthy and unhealthy individuals; male, female Recall or extrapolation of baseline G6PD activity at future time (see note) e.g. *P. vivax* infection	Same + stand-alone haemoglobin 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 G6PDd. Therefore, re-testing after 1 year of age may be warranted.
Target use setting	Basic laboratory settings (Level 2), including mobile units – referrals 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 according to Ghani et al and Maputo Declaration
End user	Trained laboratory technician	Same + trained health care workers	
Performance			
Analyte	Whole blood G6PD activity and haemoglobin concentration	RBC G6PD activity (see note), haemoglobin concentration and DNA sequences for common variants	Determination of RBC G6PD activity is preferable but may pose significant technical challenges and therefore, should not be prioritized over ease-of-use, including portability and price. For additional analytes to G6PD, specifications need to be developed separately
Limit of quantification	G6PD < 0.8 U/gHb	G6PD < 0.4 U/g Hb; for a specimen of 12g/dL haemoglobin (equivalent to commonly used commercial reference methods)	Limit of quantification is the smallest concentration of analyte in a test sample that we can determine with acceptable repeatability and accuracy; the enzyme activity of specimens in

Characteristic	Acceptable	Desirable	Notes
			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 venous (EDTA anticoagulated)	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 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 with data in Pfeffer et al.(PLoS Med. 2020 May 14;17(5):e1003084) Differences proposed will not, even in the worst-case scenario, lead to classification of deficient as normal or normal as deficient.
Type of analysis	Quantitative		
Interpretation	Numerical hardware reader in U/gHb +/- % of normal G6PD activity (proprietary device/instrument or smart phone application) – no calculations required		Ideally possible to set adjusted male median (AMM)/100% level and thresholds (e.g. 30% AMM, 70% AMM), and have the device show interpretation directly without the need for the operator to use a crosswalk (e.g. “normal”, “intermediate”)
Test procedure	Sample prep steps 2 • Reagents reconstitution: easy to do or ready to use	Sample prep steps 0–1 • Reagents reconstitution: ready to use	

Characteristic	Acceptable	Desirable	Notes
	• Need to transfer precise volume: Acceptable but ideally not required • Time steps: ≤ 3 with the potential for digitally guided workflows and built-in timers to reduce user errors on timed steps • Time to result: ≤ 30 minutes • Results validity: stored image or results • Invalid rate: < 4% invalid results with correct use by operator	• Need to transfer precise volume: not required • Time steps: ≤ 2 with the potential for digitally guided workflows and built-in timers to reduce user errors on timed steps • Time to result: ≤ 10 minutes • Results validity: stored image or results • Invalid rate: < 2% invalid results with correct use by operator	
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	≤ 2 days 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)	≤ 1 day 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 4–35 °C, humidity 75% + 5%.; tolerates freezing and brief periods > 40–45 °C; any associated equipment must meet or exceed these requirements.	> 18 months at 4–40 °C, 80% + 5%; tolerates freezing and brief periods > 45 °C; any associated equipment must meet or exceed these requirements.	
Specimen transport conditions	≥ 48 hrs at 2–8 °C	≥ 72 hours at ambient temperature (~10–35 °C)	
Specimen capacity and throughput	≤ 10–30 minutes run time ≥ ~ 2–6 results/hour ; single use test	Random access, batch in ≥ 5; ≤ 10 minutes run time ~ ≥ 30 results/hour	
QA/QC	Assurance of correct operation with minimal user-required QC procedure	Same + external quality assessment material compatible	

Characteristic	Acceptable	Desirable	Notes
	Positive control and negative control sold separately or included in kit Calibration control for instruments		
Safety	Universal precautions for a POC /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 QC results (pending upload)	≥ 5000 patient results (pending upload) ≥ 500 QC 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 that data when back online automatically	Same + the reader shall transmit automatically (without user action) in the background when back online	
Data exchange standards	The reader supports at least one of the following formats: HL7, FHIR, or JSON	The reader supports all of the following formats: HL7, FHIR, and JSON	
Data destination	Saved on device/instrument and/or computer interface	Health program shall be able to choose the destination of the reader's data – i.e. compatibility with standard national HMIS data systems, country specific electronic medical records or dedicated G6PD databases	
Data ownership	in compliance with local authorities and regulations, the health program 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,		

Characteristic	Acceptable	Desirable	Notes
	and policies of their settings and best practices, the reader shall provide configurable features so that personal data can be: a. gathered transparently to users and patients, including consent b. collected and processed only for purposes compatible with the health program's purposes c. limited to what is relevant and necessary d. collected accurately e. stored in identifiable form no longer than necessary f. 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 ID identifiers, if required; patient identifier codes entered manually	Same + patient identifier codes entered by scanning 1D and 2D barcodes	
Contextual data collected	Time and date of test	Location of testing site (if enabled by the health program) and ambient temperature	
Portability	Desktop; mains power; surge protection	Handheld or portable (< 3kgs); 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 and warranty	< US$ 10; instrumentation < US$ 2000; lifespan - ≥ 24 replacement month warranty and repair policy ≥ 7 years	< US$ 5 / test and instrumentation < US$ 1000; lifespan - ≥ 24-month replacement warranty and repair policy ≥ 10 years	Significantly higher price than malaria rapid test acceptable, as one-off use only per person. Higher prices for instruments could be acceptable if platforms are multipurpose. Test developers would also want to

Characteristic	Acceptable	Desirable	Notes
			consider instruments/devices being free of charge when certain volumes of tests are purchased
Product registration	Regulatory approval in malaria endemic countries and those with high prevalence of G6PD deficiency (≥ 3%) and WHO prequalification		Collaborative review procedures for country assessments to be considered to improve efficiency; interim measures such as The Global Fund Expert Review Panel for Diagnostics (ERPD) approval 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 according to Ghani et al.*(1)* and the Maputo Declaration *(2)*

Characteristics	Level 0	Level 1	Level 2	Levels 3 and 4
Description	In the community or home	Lowest level of healthcare system with a laboratory	First level of referral healthcare and laboratories	Second and higher levels of referral healthcare and laboratories
Examples of locations	In homes, health fairs, health posts, clinics with no lab, pharmacies	Health centres (Africa), rural health centres (Asia and Latin America)	Hospitals (Africa), urban health clinics (Asia and Latin America), clinical labs 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 hav refrigeration	Available
Clean water	Not reliably available	Not reliably available	Available	Available
Physical lab infrastructure and lab equipment	No laboratory	Not all facilities have labs.If present, minimal lab (e.g. microscope, centrifuge) or moderate lab (see level 2 description)	Moderately equipped lab (e.g. additional equipment for basic chemistry and manual immunoassays)	Well-equipped laboratories (e.g. automated and advanced equipment)
Personnel	Community healthcare worker, nurse, family member, pharmacist, traditional medicine practitioner	Nurses, sometimes physicians, laboratorians with a range of training	Nurses, physicians, moderate and well-trained laboratorians	Nurses, physicians, well-trained laboratorians

References

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2. Maputo Declaration on Strengthening of Laboratory Systems: https://www.who.int/publications/m/item/the-maputo-declaration-on-strengthening-of-laboratory-systems