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SARS-CoV-2 antigen rapid diagnostic tests for professional use and self-testing

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Abbreviations

ANOVA	analysis of variance
Ct	cycle threshold
HAMA	human anti-mouse antibody
IFU	instructions for use
IMDRF	International Medical Device Regulators Forum
ISO	International Organization for Standardization
IVD	in vitro diagnostic
LOD	limit of detection
POC	point of care
RDT	rapid diagnostic test
RT-PCR	reverse transcriptase polymerase chain reaction
TGS	Technical guidance series
VoC	variant of concern
WHO	World Health Organization

A Introduction

The purpose of this document is to provide technical guidance to in vitro diagnostic (IVD) medical device manufacturers that intend to seek WHO prequalification of rapid diagnostic tests (RDTs) for the detection of SARS-CoV-2 antigen for point of care professional use and self-testing.

The current version of this document does not address the requirements for accompanying quality control material. However, if quality control material is provided by the manufacturer (with the product or separately), it should demonstrate that the IVD is functional and performs as claimed (see ISO 15198 (1)).

For this document, the verbal forms used follow the usage described below:

- "shall" indicates that the manufacturer is required to comply with the technical specifications;
- "should" indicates that the manufacturer is recommended to comply with the technical specifications, but it is not a requirement;
- "may" indicates that the technical specifications are suggested methods to undertake the testing, but not requirements.

A documented justification and rationale shall be provided by the manufacturer when the WHO prequalification submission does not comply with the required technical specifications outlined in this document.

For WHO prequalification purposes, manufacturers shall provide evidence in support of the clinical performance of an IVD to demonstrate that reasonable steps have been taken to ensure that a properly manufactured IVD, being correctly operated in the hands of the intended user, will detect the target analyte consistently and fulfil its indications for use.

Where possible, WHO analytical and clinical performance study requirements are aligned with published guidance, standards and/or regulatory documents. Although references to source documents are provided, in some cases WHO prequalification has additional requirements.

WHO prequalification requirements summarized in this document do not extend to the demonstration of clinical utility, i.e., the effectiveness and/or benefits of an IVD, relative to and/or in combination with other measures, as a tool to inform clinical intervention in a given population or healthcare setting. To demonstrate clinical utility, a separate set of studies is required.[1] Clinical utility studies usually inform programmatic strategy and are thus the responsibility of programme managers, ministries of health and other related bodies in

[1] See the International Medical Device Regulators Forum (IMDRF) document GHTF/SG5/N6:2012 Clinical Evidence for IVD medical devices – Key Definitions and Concepts for more information: http://www.imdrf.org/docs/ghtf/final/sg5/technical-docs/ghtf-sg5-n6-2012-clinical-evidence-ivd-medical-devices-121102.pdf

individual WHO Member States. Such studies do not fall under the scope of WHO prequalification.

B Other guidance documents

This document should be read in conjunction with other relevant WHO guidance documentation, including:

- Technical guidance series for WHO prequalification – Diagnostic Assessment available at https://extranet.who.int/pqweb/vitro-diagnostics/guidance-documents
- WHO Prequalification "Instructions for Compilation of a Product Dossier", WHO document PQDx_018 (2)
- WHO Target product profiles for priority diagnostics to support response to the COVID-19 pandemic v.1.0 28 September,2020 (3)
- WHO Diagnostic testing for SARS-CoV-2: interim guidance, 11 September 2020 (4)
- WHO Laboratory biosafety guidance related to coronavirus disease (COVID-19): interim guidance, 13 May 2020 (5)
- WHO Antigen-detection in the diagnosis of SARS-CoV-2 infection using rapid immunoassays: interim guidance (6)

C Performance principles for WHO prequalification

C.1 Intended use

An IVD intended for WHO prequalification shall be accompanied by a sufficiently detailed intended use statement. This should allow an understanding of at least the following:

- The type of assay
- what the IVD medical device detects;
- its function (e.g. screening, diagnosis or aid to diagnosis;
- whether or not it includes automated components or is intended to be used with automated instruments;
- what the IVD medical device reports (e.g., qualitative test, semi-quantitative);
- the type of specimen(s) (e.g., nasopharyngeal swabs, oropharyngeal swabs, nasal swabs etc) required and collection method (e.g. swabs provided with kit, professional or self-collected swab);
- target population (on whom the IVD medical device is used)

- The intended use environment and the intended user (e.g. trained healthcare provider[2], lay user[3], in a laboratory setting, in a community setting or at point of care (POC) [4], or self-testing by lay users)

C.2 Diversity of specimen types, users and testing environments and impact on required studies

For WHO prequalification submission, clinical performance studies shall be conducted using the specimen types (e.g., nasal swabs, oropharyngeal swabs, nasopharyngeal swabs claimed in the instructions for use (IFU).

Prequalified IVDs in low- and middle-income countries are likely to be used by laboratory professionals either in laboratories or at POC, or by healthcare workers/lay providers trained in the use of the test at POC, or self-testing by lay users (additional validation requirements apply, see chapter 4.02.05). Depending on the intended use of the IVD, analytical and clinical performance studies shall be designed to consider the diversity of knowledge and skills of potential IVD users, and the likely operational settings in which testing is likely to occur. It is a manufacturer's responsibility to ensure that the risk assessment for an IVD reflects the intended operational settings, including service delivery complexity and the likely intended user conducting the test.

Laboratory demonstration of equivalence between specimen types without evidence of clinical validation is insufficient). For example, studies that comprise the testing of left-over/repository specimens by research and development staff at a manufacturer's facility shall not, on their own, be considered sufficient to meet many of the performance requirements summarized in this document. Thus, if multiple specimen types are claimed in the intended use (e.g nasal swabs, nasopharyngeal swabs, and oropharyngeal swabs) clinical performance shall be evaluated for each claimed specimen type. If the swabs supplied with kit originate from different sources, equivalence of the swabs shall be demonstrated.

C.3 Applicability of supporting evidence to IVD under review

Performance studies shall be undertaken using the specific, final (locked down) version of the IVD intended to be submitted for WHO prequalification. For WHO prequalification, design lock-down is the date that final documentation, including quality control and quality assurance specifications, is signed off and the finalized method is stated in the IFU. Where this is not possible, a justification shall be provided, and additional supporting evidence may

[2] Medical technologists, medical laboratory technicians or similar, who have received a formal professional or paraprofessional certification or tertiary education degree.

[3] Any person who performs functions related to healthcare delivery and has not received a formal professional or paraprofessional certification or tertiary education degree. Lay providers and lay users may be used interchangeably in this document.

[4] Point-of-care (POC) in-vitro diagnostic testing refers to decentralized testing that is performed by a minimally trained healthcare professional near a patient and outside of central laboratory testing facilities. It does not refer just to sample collection procedures. In some jurisdictions (e.g., European Union), the concept "near patient testing" is used instead of "point of care testing". Either term may be used in the intended use statement.

also be required. This may occur in the case of minor variations to design where no impact on performance has been demonstrated (see WHO document Reportable Changes to a WHO prequalified in vitro diagnostic medical device (7)).

If the methods section of the IFU has been changed in any way, both the study protocol provided to a laboratory for the clinical performance studies/IFU provided in the observed trained user study as outlined in Part 2 of this document, and that in the final version of the IFU intended for users shall be provided with the submission to WHO prequalification.

The version of the IFU used for analytical and clinical performance studies shall be stated. If the test procedure in the IFU is changed in any way after completing performance verification and validation studies the change shall be reported to WHO prequalification, including a rationale for the change, and an explanation of why the study results support the claimed performance.

Specific information is provided in this document for the minimum number of lots required for each study. Where more than one lot is required, each lot shall comprise different production (or manufacturing, purification, etc.) runs of critical reagents, representative of routine manufacture. It is a manufacturer's responsibility to ensure, via risk analysis of the IVD that the minimum numbers of lots chosen for estimating performance characteristics considers the variability in performance likely to arise from the interlot diversity of critical components and their formulation or from changes that could occur during the assigned shelf life of the IVD.

The true clinical status (presence of absence of active SARS-CoV-2 infection) status shall be determined using a suitable molecular reference method. For WHO purposes this should be a nucleic acid amplification test (NAT) that currently is at a developed stage of technical capability based on the relevant consolidated findings of science, technology and experience (commonly referred to as state of the art). Justification for the choice of method, shall be provided. Manufacturers intending to submit clinical studies that were conducted and assessed as part of the WHO EUL procedure are recommended to contact WHO in advance of the submission.

Estimation (and reporting) of IVD performance shall include the rate of invalid results and the 95% confidence interval around the estimated values for key performance metrics, as appropriate.

For certain analytical performance studies, it may be acceptable to use contrived specimens e.g., where normal human specimens or artificial matrix have been spiked with human specimens containing SARS-CoV-2 or SARS-CoV-2 cell culture, or with recombinant material. However, clinical performance studies reported according to Part 2 shall be based on testing in natural specimens.

D Table of requirements

WHO requires that a product dossier is submitted in the "Table of Contents" (ToC) format, described in the International Medical Device Regulators Forum (IMDRF) document IMDRF/RPS WG/N13 FINAL:2019 (Edition 3) (8). In the tables below, the chapters and

subheadings are labelled and numbered according to IMDRF ToC format. As the IMDRF ToC is comprehensive in nature, not all subheadings are required for WHO prequalification and are excluded. As a result, the subheading numbering in the tables below is not always continuous (e.g., 3.1.1, 3.1.3, etc). This has been done to maintain consistency between sections required in a product dossier for WHO prequalification assessment and the corresponding numbering defined in the IMDRF ToC format.

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3.06.04d	Result interpretation study

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4.02.03d	Observed untrained user study

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Part 1: IMDRF ToC Chapter 3 Analytical performance and other evidence

	IMDRF ToC Chapter heading and aspect	Testing requirements	Notes on testing requirements	Source Documents
236.	**3.05.01: Stability of specimen(s)**			
237.	Specimen collection, storage and transport	1 Real time studies shall be determined for each specimen type taking into account: • storage conditions (duration at different temperatures, temperature limits, freeze/thaw cycles; (see note 2); • specimen collection and/or transfer devices intended to be used with the IVD; • transport conditions; • intended use. 2 Testing in a minimum of 10 specimens from different individuals (see note 3). 3 For qualitative RDTs specimens shall be weakly reactive: 2 – 3 x limit of detection (LOD). 4 Testing shall be conducted using 1 lot.	1 Evidence shall be provided which validates the maximum and minimum allowable times between specimen collection, processing of the specimen and its addition to the IVD. 2 The likely environmental conditions at the site of expected specimen collection shall be taken into consideration for the following: • Stability on the swab – time between taking the swab and putting it into the extraction buffer or transport medium; • Stability in the extraction buffer and transport medium (if used); • Stability if stored frozen and number of freeze-thaw cycles. 3 Swabs from different individuals, tested negative for SARS-CoV-2, may be spiked with whole virus. 4 Unless all specimens are expected to be processed as fresh samples within a specified timeframe, the RDT performance shall be established using specimens stored under different conditions and at the beginning and end of a stated period. 5 In case the use of archived/stored specimens is considered for part 1 or part 2 of this document, evidence of specimen stability shall be demonstrated	
238.	**3.05.02: Validation of specimens**			

	IMDRF ToC Chapter heading and aspect	Testing requirements	Notes on testing requirements	Source Documents
239.	Demonstration of equivalence between specimen types	1 Equivalence of specimen types shall be demonstrated (see notes 1 and 2) using: • 1 weakly reactive specimen for each claimed specimen type (2 to 3 x LOD); • 3 moderately reactive specimens for each claimed specimen type (5 to 7 x LOD); • 1 negative specimen of each claimed specimen type. 2 If performance in specimen types is not equivalent, the level of agreement shall be stated and the impact this will have on each subsequent performance claim shall be fully understood and described (see note 3). 3 If equivalence is claimed between different types or manufacturers of swabs (for the collection of the same specimen type), testing shall be conducted with each swab type as in point 1 above. 4 Using 1 lot of product and swabs.	1 If weakly reactive clinical specimens are not available, extracted specimens of each type from individual negative donors may be spiked with: • a small (less than 5% v/v) amount of a known strongly positive extracted specimen; • or cultured whole virus. 2 Specimens of all claimed types shall be taken through the whole assay procedure from specimen collection, transport media and storage if appropriate, and the final test procedure. 3 The established relationship between IVD performance in claimed specimen types (e.g., anterior nasal and NP swabs) shall be considered in the design of subsequent analytical studies. For example, if the studies show that one or more of the claimed specimen types are equivalent, then not all specimen types need to be tested in some of the subsequent studies (where indicated). 4 Results from the non-reactive specimens of different specimen types should be analysed to evaluate potential differences that could imply potential false reactivity in a larger testing population.	TGS-3 (9) European Common specifications (10)
240.	**3.05.03 Metrological traceability of calibrator and control material values**			
241.	Metrological traceability of calibrator and	1 The manufacturer should demonstrate that the controls offered with the kit and reference material used in the validation studies are traceable to the WHO International	1 The version of the international standard used shall be stated	ISO 17511 (11) CLSI EP 30 A (12)

	IMDRF ToC Chapter heading and aspect	Testing requirements	Notes on testing requirements	Source Documents
	control material values	Standard for SARS-CoV-2 antigen (or a secondary standard calibrated against it		WHO TRS (13)
242.	**3.05.04 Accuracy of Measurement**			
243.	**3.05.04.02 Precision (Repeatability & Reproducibility)**			
244.	Repeatability & reproducibility	1 Precision (repeatability and reproducibility) shall be estimated using panels of at least the following spiked specimens (see note 2): • 1 non-reactive specimen; • 1 weak reactivity specimen (2 to 3 x LOD); • 1 medium reactivity specimen (5 to 7 x LOD). 2 Each panel member shall be tested: • In 5 replicates per test; • Over 5 days (not necessarily consecutive) with one run per day (alternating morning/afternoon); • Repeated in total with 3 different lots (see note 5); • at each of 3 different sites. 3 For all precision studies, the effect of operator-to-operator variation on IVD performance shall be included as part of the precision studies (see notes 7 and 8). 4 Testing shall be conducted: • By users representative of intended users, not all staff members of the manufacturer; • Unassisted;	1 Studies shall be statistically designed and analysed to identify and isolate the sources and extent of any variance. • Within or between -run, -lot, -day, -site, -users, • For purely qualitative assays the results are likely to be defined in terms of proportions of specimens detected (hit rate); • Users shall be blinded to the expected results at all times. 2 The testing panel shall be the same for all times, operators, lots, and sites • The panel may be prepared by spiking a pool of extracted negative specimens or a certified synthetic analogue of the extracted specimen. 3 The whole test procedure from elution from the swabs to the final result shall be utilised. • Swabs may be dosed with an appropriate amount of the relevant panel member. • Only 1 type of swab needs to be used for reproducibility studies, but repeatability must be studied with all. 4 Graded results shall be reported to detect differences in the reactivity of the test line.	EN 13612 (14) CLSI EP05-A3 (15) CLSI EP12-A2 (16)

	IMDRF ToC Chapter heading and aspect	Testing requirements	Notes on testing requirements	Source Documents
		• Using only those materials provided with the RDT (e.g., IFU, labels and other instructional materials). 5 If swabs are obtained from different sources then repeatability studies shall be performed with each (see note 3).	5 Each lot shall comprise different production (or manufacturing, purification, etc.) runs of critical reagents (see section C.3). 6 To understand irregularities in results obtained, at least 2 of the 3 lots shall be tested at each of the 3 testing sites. 7 The effect of operator-to-operator variation on IVD performance may also be considered as a human factor when designing robustness studies (see section 3.06.04 Usability/human factors) and may be addressed as part of clinical studies in representative populations (see Part 2). 8 Users shall be selected based on a pre-determined and contextually appropriate level of education, with literacy and auxiliary skills that will challenge the usability of the RDT and reflect the diversity of intended users and operational settings. These characteristics shall be detailed in the study report. 9 The percentage of correctly identified, incorrectly identified and invalid results shall be tabulated for each specimen and be separately stratified according to each site, lot, etc. This type of analysis is especially important for RDTs that may not have results with any numerical values.	
245.	**3.05.05 Analytical sensitivity**			
246.	Limit of detection (LOD)	1 The LOD of SARS-COV-2 antigen RDTs shall be determined relative to the international standard or to secondary standard metrologically traceable to it (see note 1) 2 The determination should comprise a minimum of 20 replicate tests of an 8-member dilution panel.	1 The version of the international standard used shall be stated. 2 The LOD is defined as the lowest concentration of analyte that can be consistently detected	CLSI EP 12 CLSI EP17-A (17) ISO 17511 (11)

	IMDRF ToC Chapter heading and aspect	Testing requirements	Notes on testing requirements	Source Documents
		3 The replicate testing shall be conducted on 3 different days. 4 Testing shall be conducted using a minimum of 2 different lots. 5 LOD shall be estimated for all specimen types. 6 The whole test procedure from elution from the swabs to the final result shall be utilised. 7 The impact on variants of concern (VoCs) on LOD shall be evaluated (see note 5).	• Typically, in > 95% of samples tested under routine clinical laboratory conditions and in a defined specimen type. 3 Determination shall be according to an approved statistical method (e.g. see source document EP 12 or 17). • For qualitative assays the logistic fit method is acceptable. 4 The analyte concentration may be prepared by spiking a pool of extracted negative specimens or a certified synthetic analogue of the extracted specimen • Swabs may be dosed with an appropriate amount of the relevant dilution of the analyte; • Only one type of swab needs to be used if equivalence has been demonstrated. 5 For genetic variants for which an international standard is not available a dilution series of well characterized virus isolates spiked into clinical matrix may be used and results stated in comparison with other SARS-CoV-2 antigen tests .	European common specifications (10)
247.	**3.05.06 Analytical specificity**			

	IMDRF ToC Chapter heading and aspect	Testing requirements	Notes on testing requirements	Source Documents
248.	3.05.06a Potentially interfering substances	1 The potential for false results (false non-reactive and false reactive results) arising from interference from at least, but not limited to, the substances/conditions listed below shall be determined (see note 1): 2 Testing shall be undertaken in SARS-CoV-2 antigen non-reactive and SARS-CoV-2 antigen reactive specimens (see note and 6; unspiked or spiked), with each potentially interfering substance at the highest levels found in individuals (see note). 3 Testing shall be performed: • in 1 lot (see note 4). • in 3-5 replicates • in one specimen type	1 The risk assessment conducted for the RDT should identify substances/conditions where the potential for interference can reasonably be expected with the analyte to be detected in the areas of intended use: • By conducting and documenting appropriate risk assessment testing can be performed on specimens spiked with the substances/ conditions identified as likely to be significant and testing of potentially irrelevant substances/conditions avoided. • Not by simple reliance on published lists of such compounds and conditions, which might be of limited relevance to this analyte; • Under some circumstances stringent risk evaluation might eliminate the necessity to test some of the items in the test requirements column (see paragraphs above) but any such decision shall be documented in the submissions to WHO and considered in the risk-benefit statements. • Any effect must be evaluated against the probability of that effect occurring, given the prevalence of that substance in each of the populations intended to be tested and the clinical significance of the effect. 2 Any observed interference or cross-reactivity shall be investigated and performance limitations of the RDT reported in the IFU.	European common specifications (10) CLSI EP07 (18) CLSI EP37 (19) ISO 14971 (20) U.S FDA (20)
249.	Endogenous substances	1 Substances/conditions expected to be found in the specimen types claimed e.g. • Mucin: bovine submaxillary gland, type I-S; • blood (human) ; • Antibodies, e.g. human anti-mouse (HAMA) 2 5 to 10 specimens per from different individuals for each substance/condition shall be tested		
250.	Exogenous substances	1 Medicines, relevant to the populations intended to be tested: • Nasal sprays or drops; • Nasal corticosteroids; • Nasal gel; • Throat lozenges, oral anaesthetic and analgesic;		

	IMDRF ToC Chapter heading and aspect	Testing requirements	Notes on testing requirements	Source Documents
		• Anti-viral drugs; • Anti-parasitic drugs (e.g. malaria, treponema) • Antibiotic, nasal ointment; • Antibacterial, systemic; • Biotin (see note 7).	3 Results shall be reported with respect to each condition and not be reported as an aggregate of the total number of specimens tested in the study 4 The lot used in testing shall be the same lot as used in section 3.05.05 LOD studies. 5 The methods and concentrations used for interference studies shall be validated so that any effect of clinical importance would be detected: • The specimens for analysis may be prepared by spiking a pool of extracted negative specimens or a certified synthetic analogue of the extracted specimen with both SARS-CoV-2 and the interfering material of interest. • Whether the whole test procedure from a dosed swab to result or merely from the spiked extract should be performed may be decided by risk evaluation of the likelihood of interference at the extraction step. 6 Interference studies shall be performed with SARS-CoV-2 antigen reactive specimens with a concentration near the LOD. 7 For interference studies, if biotin is commonly used as a supplement and the technology of the test employs streptavidin, then biotin levels of up to 3500 ng/ml should be tested as part of this study. 8 For cross reactivity studies, where clinical specimens from individuals with the disease state to be tested are unavailable, a negative specimen shall be spiked with the organism of interest to a high concentration (a minimum of	
251.	3.05.06b Cross-reactivity	1 The potential for false results arising from cross-reactivity (see note1) shall be determined for at least 5 to 10 for each of the following microorganisms: • Human coronavirus 229E, Human coronavirus OC43, Human coronavirus HKU1, Human coronavirus NL63 • SARS-coronavirus • MERS-coronavirus • Adenovirus (e.g. C1 Ad. 71) • Human Metapneumovirus (hMPV) • Parainfluenza virus 1-4 • Influenza A, Influenza B • Enterovirus (e.g. EV68) • Respiratory syncytial virus • Rhinovirus • Chlamydia pneumoniae • Haemophilus influenzae • Legionella pneumophila • Mycobacterium tuberculosis*		

	IMDRF ToC Chapter heading and aspect	Testing requirements	Notes on testing requirements	Source Documents
		• Streptococcus pneumoniae • Streptococcus pyogenes • Bordetella pertussis • Mycoplasma pneumoniae • Pneumocystis jirovecii (PJP)*[5] • Candida albicans • Pseudomonas aeruginosa • Staphylococcus epidermis • Streptococcus salivarius • Pooled human nasal wash - to represent diverse microbial flora in the human respiratory tract • other unrelated conditions known or suspected to cause cross-reactivity in SARS-COV-2 antigen immunoassays (see note 1); 2 Testing shall be conducted in 1 specimen type	10^5 plaque forming units/mL for viruses and 10^6 colony forming units/mL for bacteria).	
252.	**3.05.07 High dose hook effect**			
253.	Prozone/High dose hook effect	1 The potential for a high dose hook effect (prozone) shall be determined: • Using at least 3 different lots • Spiking negative matrix with a high antigen concentration (approximately 20 000 x LOD)	1 Prozone effect may be investigated using high concentrations of SARS-CoV-2 antigen reactive specimens (cultured virus or recombinant antigen).	Butch, AW (22)

[5] * only applicable if lower respiratory matrixes are claimed (e.g. sputum)

	IMDRF ToC Chapter heading and aspect	Testing requirements	Notes on testing requirements	Source Documents
		2 If there is evidence of a prozone effect, this information shall be added to the IFU, and mitigation actions shall be described. 3 Testing shall be conducted in 1 specimen type		
254.	**3.05.09 Validation of Assay Cut-off**			
255.	Establishment of reader cut-off	1 For RDTs provided with a reader, the way in which the reader has been designed to differentiate reactive specimens from non-reactive specimens shall be described in detail and demonstrated. 2 If both manual and automated digital read-out versions of the reader are available, equivalence of the 2 modes should be demonstrated.	1 If the manufacturer supplies a reader for use with the IVD, safety and performance data shall be provided in the dossier with and without the use of the reader.	
256.	**3.05.10 Validation of the assay procedure**			
257.	3.05.10a Validation of assay parameters	1 Evidence shall be provided on how any parameters specified in the IFU were determined, validated, and verified. 2 The parameters specified in the IFU commonly include the following, but the actual requirement is assay dependent and must be ascertained for each IVD: • Allowable reading time (see note 3); • Time interval between opening the pouch and starting the assay; • Extraction and mixing times and methods; • Volumes, including numbers of drops; • Temperatures e.g., operating temperature range and • Humidity.	1 These parameters may be investigated as part of 3.06.04 Usability/Human factors, below. 2 The intent of parameter validation is to demonstrate that no combination of small but defined variations in the parameters of the protocol will result in the IVD failing to meet any of the manufacturer's claims i.e., the assay is robust. • "designed experiments" – changing more than one parameter at once – are more appropriate than single changes with all other parameters held constant. 3 For RDTs where a reading interval is specified, validation of critical time points shall be provided: • The result at the minimal allowable time and;	Montgomery DC, (24) PQDx_018 (2) USP (25)

	IMDRF ToC Chapter heading and aspect	Testing requirements	Notes on testing requirements	Source Documents
		3 Using 2 lots (one freshly made lot and one lot of IVD towards the end of the assigned shelf life) 4 Specimen panel to be tested in triplicate shall be as follows: • 1 non-reactive specimen • 1 weak reactivity specimen (approx. 2 to 3 x LOD) • 1 medium reactivity specimen (approx. 5 to7 x LOD).	• The result at the maximal allowable time.	
258.	3.05.10b Validation of the control line or dot	1 The flow device shall have a procedural control (see note 1). 2 The nature of the procedural control shall be explained (see note 2).	1 The extent to which any control line or dot corresponds to a valid test shall be demonstrated. 2 The precise meaning of the control line must be stated in the IFU of the device, e.g. evidence of: • Reagent addition and flow; • Specimen addition and flow; • Correct volumes being added; • Correct operation of the device; • Correct functionality of all reagents.	ISO 15198 (1)
259.	**3.06 Other Studies**			
260.	**3.06.04 Usability/human factors**			
261.	3.06.04a Flex/ Robustness studies	1 The intent of this study is to demonstrate that no combination of small but defined variations in the parameters of the protocol will result in the IVD failing to meet any of the manufacturer's claims i.e., the assay is robust. 2 Specimen panel to be tested in triplicate shall be as follows: • 1 non-reactive specimen	1 Refer to WHO document PQDx_018 "Instructions for compilation of a product dossier" for other flex studies that may be relevant, taking into consideration the broad range of operational and environmental conditions consistent with intended use in resource limited settings. 2 The factors listed should be investigated in ways that not only reflect, but also exceed, likely operating conditions in	ISO 14971 (20) PQDx_018 (2) IEC 62366 (26)

IMDRF ToC Chapter heading and aspect	Testing requirements	Notes on testing requirements	Source Documents
	• 1 weak reactivity specimen (approx. 2-3 x LOD) • 1 medium reactivity specimen (approx. 5-7 x LOD). 3 The influence of the following factors on expected results (both reactive and non-reactive) shall be considered based on the risk-assessment conducted, for example but not limited to: • time between opening packaging or preparing reagents and starting the assay; • specimen collection; • mixing times and methods; • specimen volume; • reagent volume provided and used; • specimen dilution factor; • reading time; • operating temperature, pressure, and humidity. 4 Ruggedness shall be determined: • RDT sturdiness including robustness of packaging and labelling (see note 4). RDT in final packaging shall be subjected to drop-shock testing; • Permanence of component labels: print legibility, adhesiveness (see note 4 and 5); • Effects of lighting and humidity (see note 3); • Residual volumes and characteristics of liquids (potential evaporation, pH changes, microbial growth, antimicrobial efficacy).	low- and middle-income countries so that the limitations of the device can be understood. For example, in addition to investigating deviations of temperature within those claimed in the IFU, temperature ranges should be investigated that exceed those of claimed operating conditions and which cause test failure (incorrect/invalid results) 3 The resilience of labels (e.g., strength of attachment, print stability, legibility over time, damp tolerance) shall be evaluated 4 The impact of lighting can be multiple: • The impact of lighting on an unstable material, which can affect preparation, incubation and reading times and conditions; • Bright light causing fading of labelling; • Inability to correctly view the result. 5 The factors should be investigated using “designed experimentation” so that potential critical interactions between them can be understood e.g., the effect of low or high operating temperature with low or high volume of specimen at an incorrect reading time. 6 Some of these parameters/factors may be investigated as part of 3.05.10a Validation of assay parameters.	

	IMDRF ToC Chapter heading and aspect	Testing requirements	Notes on testing requirements	Source Documents
		5 Review of instrumentation (if applicable and based on a risk assessment) including: • ruggedness (see above and note 5); • impact of dust and mould on componentry (e.g., optics if applicable). 6 Studies shall be conducted in the most challenging specimen type 7 For RDTs intended for **self-testing** the impact of additional conditions on the test result shall be considered: • The influence of mixing the swab in elution buffer (or other reagents): all extremes from not-mixing to vigorous shaking, including generating bubbles and intermediate mixing (i.e. swirling 1 or 2 times) should be addressed. • Variations (delay/disturbance) in operational steps, e.g. extraction procedure (time of swab in extraction buffer and/or number of rotations of swab in extraction buffer). • Placement of the test device on non-level surface. • The impact of different light sources on the visual reading of the control and test lines. • The effect of moving the test device while it is running (e.g. relocating to another surface or dropping it)		
262.	3.06.04b Usability: Label compre-hension study (including IFU)	1 Testing shall be undertaken to assess the ability of intended users to correctly comprehend key messages from packaging and labelling: • Understanding key warnings, limitations and/or restrictions to its use;	1 Requirements listed may be investigated as a separate studies or included as part of the results interpretation studies and/or clinical studies. 2 Testing may be conducted using questionnaire-based surveys.	

	IMDRF ToC Chapter heading and aspect	Testing requirements	Notes on testing requirements	Source Documents
		• Proper test procedure; • Test result interpretation; • Using only the information available to all users (IFU and any job aid). 2 Studies shall include at least 15 intended users in their usual working environment		
263.	3.06.04c Usability: Results interpretation study	1 Intended users shall interpret the results of contrived RDTs (e.g., static/pre-made tests) to assess their ability to correctly interpret pre-determined test results. 2 Contrived RDTs shall be made to demonstrate the following potential test results: • Non-reactive; • Range of invalid results; • Reactive; • Weak reactive. 3 Testing subjects shall consist of at least 15 intended users, in their usual working environment		European Parliament IVD regulations (32) U.S. FDA (33, 34)
264.	3.06.04d Usability	For AgRDTs intended for **self-testing**, please refer to **Part 3 a & b**		
265.	**3.06.05 Stability of the IVD**			
266.	3.06.05.01 Claimed Shelf-life & 3.06.05.03	1 Stability studies shall be conducted using the conditions expected in the environment of intended use. 2 If different reagent-container sizes are used in packs with different volumes of reagent (e.g., different volumes for packs with 25 or 50 individual devices), stability evidence (real time,	1 The lots used shall be manufactured to validated scale according to finalised protocols, including packaging, labelling, QA and QC specifications and IFU method: • each lot shall comprise different production (or manufacturing, purification, etc.) runs of critical	TGS-6 (23) ISO 23640 (27) CLSI EP25 (28**Error!**

	IMDRF ToC Chapter heading and aspect	Testing requirements	Notes on testing requirements	Source Documents
	Shipping stability	open container, in-use) shall be obtained on all variants, even if the contents of the containers are identical. 3 Lots shall be subjected to simulated "transport stress" before real time studies are undertaken on these lots: • The effects of this simulated transport shall be documented separately and in addition to the real time studies. 4 A minimum of 3 lots in final packaging shall be used (see note 1). 5 Testing in triplicate shall be undertaken using a panel of specimens of at least: • 1 non-reactive specimen; • 1 weak reactivity specimen (2 to 3 x LOD;) 6 In addition, to address specificity a minimum of 100 random non-reactive specimens shall be tested at T=0 and at the end of the claimed shelf life. 7 Stability of biocidal agents and desiccants (if applicable) shall be validated according to source document TGS-2 8 Stability of labelling shall be determined (see chapter 3.06.04)	reagents and ideally some of the reagents should be near the end of their assigned shelf lives; • The lot numbers of critical reagents in each lot of RDT shall be documented and reported. 2 If more than 1 monoclonal antibody is required (or used) to show complete detection of all claimed variants, the testing panel shall contain at least one specimen of each claimed variant to monitor each monoclonal separately during stability evaluation. 3 Changes in flow time and band development times should be reported. 4 The numbers of invalid results and repeat testing with each lot shall be reported. 5 Claims for stability shall be based on the second-last successful data point from the least stable lot 6 Accelerated studies do not replace the need for real time studies.	**Reference source not found.**) TGS-2 (29) Annex to TGS-2 (30 ASTM D4169 (31**Error! Reference source not found.**)
267.	3.06.05.02 In-use stability (open pack/open vial)	1 There shall be evidence that once the device is removed from its primary packaging, it is stable at the expected temperature and humidity ranges for a defined period of time at the beginning and end of its assigned shelf-life 2 Testing shall be performed for all labile components.	1 In-use stability of labile components shall be conducted using components in their final configuration.	TGS-6 (23) ISO 23640 (27) CLSI EP25 (28**Error! Reference**

IMDRF ToC Chapter heading and aspect	Testing requirements	Notes on testing requirements	Source Documents
	3 Liquid components, once opened, shall have a validated life and number of stated uses under environmental (including microbial) conditions expected 4 Testing shall be conducted using a minimum of 1 lot. 5 Testing in triplicate shall be undertaken using a panel of specimens of at least: • 1 non-reactive specimen; • 2 weak reactivity specimens (approx. 2 to 3 x LOD); • 1 medium reactivity specimen (5 to 7 x LOD).		**source not found.**) TGS-2 (29) Annex to TGS-2 (30) ASTM D4169 (31**Error! Reference source not found.**)

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Part 2: IMDRF ToC Chapter 4: Clinical evidence

268.	IMDRF ToC Chapter heading and aspect	Testing requirements	Notes on testing requirements	Source Documents
269.	**4.02.03 Device Specific Clinical Studies**			
270.	4.02.03a General requirements for clinical performance studies	1 Clinical sensitivity and specificity shall be determined in each claimed specimen type and for each of the population types claimed in the IFU, including, if claimed, asymptomatic individuals. 2 Testing shall be conducted: • in specimens from different geographical settings (minimum of 2 regions); • by a variety of intended users (see note 1) in the intended testing settings; • in a minimum of 2 lots at each testing site (see note 5); • Discrepant, invalid and unexpected results shall be fully evaluated so far as possible (see notes 8, 9, 10) • All claimed specimen types shall be compared with reference test results from NP swabs (see note 6, 7). The reference test shall have high sensitivity, with an initial chemical lysis step followed by solid phase extraction of the nucleic acid. The NAT and extraction method used shall be described.	1 Prequalified RDTs are generally used by trained lay users and health care workers/providers. For WHO prequalification purposes, these should be considered as the intended user rather than a trained laboratory professional. 2 Specimens for testing may include: • freshly taken, unfrozen routine specimens stored as described in the IFU; • appropriately stored, well characterized specimens that have not undergone more than one freeze-thaw cycle assuming that such handling of specimens has been validated during analytical studies (3.05.02); 3 Criteria for the selection of stored specimens shall be explained. Stored samples shall be randomized and blinded for testing. 4 The protocol shall specify the criteria for unbiased patient selection with associated risk analysis but in general there should be no exclusions except for ethical reasons: • the following information shall be reported at a minimum for each specimen tested: • The specimen type. • The specimen collection date. • Date of symptom onset.	TGS-3 (8)

268.	IMDRF ToC Chapter heading and aspect	Testing requirements	Notes on testing requirements	Source Documents
			• Clinical diagnosis (if available). • Severity of symptoms (if known) • Product name, manufacturer and product code of the reference test used • PCR test results (Ct values of SARS-CoV-2 targets and internal control) for the reference test 5 Approximately half of the specimens (for each claimed specimen type e.g. NP, OP, NS) shall be tested on different lots at each site: • The product code (not merely a product name), lot numbers and IFU version shall be reported for each clinical site. 6 Specimens for both reference test and the IVD under evaluation shall be taken within a short time interval. 7 The reference test shall be a state-of-the-art RT-PCR assay. • For devices already approved for WHO- emergency use listing the existing comparator criteria may be acceptable but any new data should be collected and reported against the criteria here. 8 Performance characteristics shall be reported using initial results only. The results of further testing of specimens with discrepant results shall be reported separately as additional information about RDT performance. 9 Problematic specimens including those with unexpected results, but which otherwise meet selection criteria for a study, shall not be systematically excluded from analysis:	

	IMDRF ToC Chapter heading and aspect	Testing requirements	Notes on testing requirements	Source Documents
			• Inconclusive results shall not be systematically excluded from the denominator data for analysis. 10 All invalid results shall be recorded. 11 Estimates of clinical sensitivity and specificity shall be reported with 95% confidence intervals for each specimen type.	
271.	4.02.03b Clinical sensitivity	1 For a symptomatic claim, at least 100 positive specimens shall be tested for each claimed specimen type from individual symptomatic patients 2 If an asymptomatic claim is made at least 40 individual specimens per specimen type from asymptomatic patients shall be tested	1 At least 50% of the results from which the clinical sensitivity is calculated shall be from fresh specimens taken from routine sequential sampling, for each claimed specimen type 2 At least 20% of specimens should have Ct >30 for at least one gene on the reference test 3 If an asymptomatic claim is made the results shall be reported separately 4 Results shall be stratified by day after symptom onset	
272.	4.02.03c Clinical specificity	1 Testing of 400 negative specimens per specimen type from symptomatic patients.	1 At least 80% of the results from which the clinical specificity is calculated shall be from fresh specimens.	European common specifications (10)
273.	4.02.03d Observed untrained user study	Only applicable to AgRDTs intended for self-testing, please refer to **Part 3c**		

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Part 3: Qualification of Usability (for RDTs intended for self-testing)

Of Note: The information must be provided in the dossier under the sections indicated -

270.	IMDRF ToC Chapter heading and aspect	Testing requirements	Notes on testing requirements	Source Documents
271.	3.06.04d Label comprehension study (including IFU)	1 Testing shall be undertaken to assess the ability of intended users to correctly comprehend key messages from packaging and labelling: • Understanding key warnings, limitations and/or restrictions to its use; • Proper test procedure; • Test result interpretation; • Using only the information available to all users (IFU and any job aid). 2 Studies shall include: • At least 100 intended users including those whose native language may not be the language of the IFU • In their usual working or home environment, not employees of the manufacturer; • From 2 geographically diverse populations to demonstrate comprehension of key messages in each user group.	1 Instructions for use and labelling should be clear and easy to understand; use of pictorial instructional material is encouraged. 2 Requirements listed may be investigated as separate studies or included as part results interpretation studies and/or clinical studies. 3 Testing may be conducted using questionnaire-based surveys.	European Parliament IVD regulations (32) EU Common specifications (10) U.S. FDA (33, 34) Backinger C (35)
272.	3.06.04d Results interpretation study	1 Intended users shall interpret the results of contrived RDTs (e.g., static/pre-made tests) to assess their ability to correctly interpret pre-determined test results.		European Parliament IVD regulations (32)

270.	IMDRF ToC Chapter heading and aspect	Testing requirements	Notes on testing requirements	Source Documents
		2 Contrived RDTs shall be made to demonstrate the following potential test results: • Non-reactive; • Range of invalid results; • Reactive; • Weak reactive. 3 Testing subjects shall consist of: • At least 100 intended users, including those whose native language may not be the IFU language; • In their usual working or home environment, not employees of the manufacturer; • From 2 geographically diverse populations to demonstrate correct interpretation of simulated test results.		EU Common specifications (10) U.S. FDA (33, 34) Backinger C, (35)
273.	4.02.03d Observed untrained user study	1 Testing in each of two geographically diverse populations of at least 90 self-testing subjects comprising of at least 30 self-testers who are reactive on the device and at least 60 who are non-reactive on the device (see notes 1, 4). 2 Each subject shall self-collect the test specimen and perform the test according to only those materials provided with the IVD (e.g. instructions for use, labels and other routinely available materials such as pictorial aids).	1 The diagnostic sensitivity and specificity (percent agreement) in the hands of the untrained user should be estimated in comparison with the results of the professionally performed RT-PCR test (see reference test requirements in section 4.02.03) on a paired nasopharyngeal or oropharyngeal swab specimen. 2 Concordance between the subject's self-test result and interpretation of the same result by a trained professional (observer) must also be reported. 3 It shall be ensured that study participants are not provided additional training by observing how	

270.	IMDRF ToC Chapter heading and aspect	Testing requirements	Notes on testing requirements	Source Documents
		3 Each such test shall be observed by a trained laboratory or healthcare professional. The observing professional shall not tutor or interact with subject conducting test but note errors and other observations about the self-tester. Observation may be conducted by way of video recording of self-testing (see notes 2, 5). 4 The observing professional shall interpret the test result in a blinded fashion and within the validated reading time stated in the instructions for use (see note 1).	healthcare providers collect the specimen for the reference test, particularly if collected from the same anatomical area as the study specimen. 4 The standard of care protocol at the study site and setting must be used to guide referral of participants to further testing or clinical management as needed. Any self-test participant who receives a reactive result should be linked to further testing and care according to the standard of care protocol at the study site and setting. 5 Particular attention should be paid to documenting the subjects' compliance with each of the factors raised during risk assessment (ISO 14971) of the process, e.g. • Paying attention to the instructions before starting; • Correct swabbing technique (e.g. insertion position, timing); • Correct specimen preparation technique once collected; • Application of correct volumes to the IVD; • Use of a timing device to use the required times for preparation and reading; • Disposal of the specimen collection accessories (e.g. swabs, liquids, extraction tubes); • Correct assignment of invalid test	

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E Source documents

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