TSS-25

Rapid diagnostic tests to detect *Neisseria gonorrhoeae* antigen

Technical specifications series for submission to WHO prequalification – diagnostic assessment

World Health Organization

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Contents

Acknowledgments

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List of contributors

A technical consultation on WHO prequalification requirements was held from 20 to 23 August 2024.

Meeting participants: Sarah Alexander, United Kingdom Health Security Agency, London, United Kingdom; Manju Bala, Regional STD Teaching, Training and Research Centre, VMMC and Safdarjang Hospital, New Delhi, India; Maria Luiza Bazzo, Federal University of Santa Catarina, Florianópolis, Brazil; Louise Causer, Kirby Institute, UNSW Sydney, Sydney, Australia; Tania Crucitti, Institute Pasteur, Antananarivo, Madagascar; Julian Duncan, London, United Kingdom; Amina El Kettani, Ministry of Health, Rabat, Morocco; Cecilia Ferreyra, FIND, Geneva, Switzerland; Matthew Hamill, Johns Hopkins University School of Medicine, Baltimore, USA, Celine Hayden, IVD Division, Health Canada, British Columbia, Canada; Lauren Johnson, Division of Microbiology Devices, CDRH, FDA, Silver Spring, USA[1]; Ellen Kersh, Laboratory Reference and Research Branch, CDC, Atlanta, USA; Mohammed Majam, Ezintsha, Johannesburg, South Africa; Philippe Mayaud, London School of Hygiene & Tropical Medicine, London, United Kingdom; Enoch Nyarko, Food and Drugs Authority (FDA), Accra, Ghana; Richard Saunders, London, United Kingdom; Heiner Scheiblauer, Paul-Ehrlich Institut, Langen, Germany; Melanie Taylor, Division of HIV Prevention, CDC, Phoenix, USA; Barbara Van Der Pol, Infectious Diseases STD Laboratory, University of Alabama, Birmingham, USA; Catherine Villegas, MSF, Geneva, Switzerland; Cheng Wang, Guangdong Center for Skin Diseases and STI Control, Guangzhou, People's Republic of China.

WHO Secretariat: Remco Peters and Teodora Wi, Global HIV, Hepatitis and Sexually Transmitted Infections Programmes; Susie Braniff, Deirdre Healy, Anne-Laure Page, Irena Prat and Ute Ströher, WHO Regulation and Prequalification Department.

This document has been developed with support from the Bill & Melinda Gates Foundation.

[1] via teleconference

Declarations of interests

All participants completed a Declaration of Interests form in advance of the meeting. Six of the participants declared interest in the topic under consideration. Louise Causer, Cecilia Ferreyra, Philippe Mayaud, Matthew Hamill, Barbara Van der Pol and Julian Duncan declared significant interests connected with their (previous) employment and/or ongoing research support for manufacturers of STI diagnostics. It could not be excluded that the declared interests may be perceived as a potential conflict of interest. Therefore, while the above mentioned persons had been invited to participate in the meeting, they participated in the discussion as technical resource people.

All remaining experts were not considered by WHO to have declared any interest that may be perceived as a potential conflict with regard to the objectives of the meeting. All the declarations, together with any updates, were made known and available to all the participants at the beginning of the meeting. All the experts participated in their individual capacities and not as representatives of their countries, governments or organizations.

Abbreviations

ATCC	American Type Culture Collection
ANOVA	analysis of variance
CFU	colony forming unit
CLSI	Clinical and Laboratory Standards Institute
IFU	instructions for use
IMDRF ToC	International Medical Device Regulators Forum Table of Contents
ISO	International Organization for Standardization
IVD	in vitro diagnostic
LOD	limit of detection
NAT	nucleic acid technology
NG	*Neisseria gonorrhoeae*
POC	point of care
RDTs	rapid diagnostic tests
ROC	receiver operator characteristic
STI	sexually transmitted infections
TGS	Technical guidance series
TSS	Technical Specification Series
US FDA	United States Food and Drug Administration
WHO	World Health Organization

A. Introduction

The document is developed for manufacturers who are interested in applying for WHO prequalification assessment, to assist in the compilation of their product dossier. The document outlines the minimum analytical and clinical performance studies to be conducted for rapid diagnostic tests (RDTs) for the qualitative detection of *Neisseria gonorrhoeae* (NG) antigen for point of care (POC) professional use in both symptomatic and asymptomatic individuals.

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 a suggested method to undertake the testing, but it is not a requirement.

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. A full list of the individual studies is provided in chapter E (Parts 1-2).

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. Clinical utility studies usually inform programmatic strategy and are thus the responsibility of programme managers, ministries of health and other related bodies in individual WHO Member States. Such studies do not fall under the scope of WHO prequalification.

B. How to apply these specifications

For the purposes of WHO prequalification, RDTs for the detection of *Neisseria gonorrhoeae* antigens shall comply with the specifications in Part 1 and Part 2 of this document.

The submission of the dossier shall be according to TSS requirements and prequalification dossier instructions "Instructions for compilation of a product dossier"[*1*].

C. Other WHO guidance documents

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

WHO prequalification documents:

- Instructions for compilation of a product dossier, WHO document PQDx_018. [*1*]
- Technical guidance series for WHO prequalification – diagnostic assessment [*2*]

WHO Global HHS programme guidelines and policies:

- Laboratory and point-of-care diagnostic testing for sexually transmitted infections, including HIV; 2023. [*3*]
- The diagnostics landscape for sexually transmitted infections; 2023. [*4*]
- Consolidated guidelines on HIV, viral hepatitis and STI prevention, diagnosis, treatment and care for key populations. [*5*]
- Guidelines for the management of symptomatic sexually transmitted infections; 2021. [*6*]
- FIND/WHO Target product profile for a rapid, low-cost diagnostic to distinguish gonorrhoea from Chlamydia infection at primary care. [*7*]

D. Performance principles for WHO prequalification

D.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 (e.g., lateral flow test);
- what the IVD medical device detects (e.g., NG antigen);
- the clinical indication and function of the IVD (e.g., diagnosis of NG infection, aid in the diagnosis of NG infection, screening of populations at increased risk of STIs);
- whether or not it includes automated components or it is intended to be used with a reader or automated instruments;
- what the IVD medical device reports (e.g., qualitative test);
- the specimen type(s) (e.g., urine, vaginal swabs, endocervical swabs, penile meatal and/or anorectal swabs);
- the specimen collection method(s) (e.g., health-care provider-collected, self-collected in a clinical setting);
- the testing population (e.g., sexually active population (including adolescents), populations at increased risk of STIs and attendees of a clinic or service for sexually transmitted infections);

- the intended user (e.g., trained laboratory professional[2] or trained healthcare workers/lay providers[3] [4] trained in the use of the IVD);
- the intended operational setting (e.g., for professional use in a POC[5] and/or laboratory setting);
- any limitation to the intended use (e.g., not for self-testing).

D.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., urine, vaginal swabs, endocervical swabs, penile meatal and /or anorectal swabs) that are claimed in the instructions for use (IFU). Prequalified RDTs are likely to be used by laboratory professionals in low- and middle-income countries, or by healthcare workers/lay users trained in the use of the test at POC. Depending on the intended use of an immunoassay, analytical and clinical performance studies shall be designed to consider not only the diversity of knowledge and skills across the population of such individuals, but also the likely operational settings in which testing will occur.

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 clinical performance study requirements summarized in this document.

D.3 Applicability of supporting evidence to IVD under review

Analytical and clinical performance studies shall be undertaken using the specific, final (locked-down design) version of the immunoassay intended to be submitted for WHO prequalification. For WHO prequalification, design lock-down is the date that final documentation is signed off, including quality control and quality assurance specifications, and the finalized method is stated in the IFU. Where this is not possible, a justification shall be provided; additional supporting evidence may 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 PQDx_121 Reportable changes to a WHO prequalified in vitro diagnostic medical device [*8*]). If the method section of the IFU has been changed in any way, both the study protocol provided to a laboratory for clinical performance

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

[3] Any person who performs functions related to healthcare delivery and has been trained to deliver specific services but has received no formal professional or paraprofessional certificate or tertiary education degree (taken from World Health Organization. (2020). Consolidated guidelines on HIV testing services, 2019 World Health Organization).

[4] Lay users do not include self-testing in the context of this document.

[5] 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 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.

studies 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 for WHO prequalification assessment.

The version of the IFU used for verification and validation studies submitted for WHO prequalification assessment 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, 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 the manufacturers responsibility to ensure, via risk analysis of the IVD, that the minimum numbers of lots chosen for estimating performance characteristics reflect the variability in performance likely to arise from the inter-lot diversity of critical components and their formulation or from changes that occur during the assigned shelf-life of the IVD. Differences found between lots during the analytical and clinical performance studies shall be reported.

Where the manufacturer supplies instrumentation required to conduct the assay, safety and performance data shall be provided in the dossier for this instrumentation. If both a visual read and an automated digital read out version of the test can be used by end users, both modes shall be utilized in each study and results/performance reported. Closed system instruments and proprietary readers are eligible.

For clinical performance studies, the true status of NG infection in symptomatic and asymptomatic individuals shall be determined using a suitable reference method. For WHO purposes the reference method should be to a level that is currently 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).

Estimation (and reporting) of IVD performance shall include the rate of invalid test results and the two-sided 95% confidence interval around the estimated values for key performance metrics, as appropriate. The cause of the invalid results should be reported if known such as sample issues (e.g., age of specimen, storage conditions, inadequate specimen volume, instrument error, operator error). Discrepant results shall be resolved as much as possible, comparison with a similar RDT is insufficient.

Data should be presented in a clear and understandable format.

It is acceptable to use contrived specimens for analytical performance studies unless otherwise specified in E) Table of requirements, part 1. Preferably well-characterized, quantified (CFU/mL or cell/mL) NG reference strains (e.g., ATCC 49226), spiked into confirmed negative matrix of the claimed specimen type.

For analytical performance studies described in part 1 it may be also possible to carefully design protocols that will generate useful data for more than one of the required studies, provided the specific criteria for each requirement are met by the study (e.g., number of replicates, concentration of analyte, lot numbers etc.). Studies which may fall in this category are indicated in the appropriate chapters of part 1.

The performance of the IVD shall be established in all claimed specimen types unless otherwise noted in the table below.

Clinical studies shall be based on testing clinical specimens only sourced from population cohorts reflective of the intended use.

E. 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) [*9*]. 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.

PART 1: IMDRF ToC CHAPTER 3 – ANALYTICAL PERFORMANCE AND OTHER EVIDENCE	
3.05	Analytical performance
3.05.01	Stability of specimen(s)
3.05.02	Validation of specimens
3.05.03	Metrological traceability of calibrator and control material values
3.05.04	Accuracy of measurement
3.05.04.02	Precision (repeatability and reproducibility)
3.05.05	Analytical sensitivity (limit of detection)
3.05.06	Analytical specificity
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3.05.06b	Cross-reactivity
3.05.06c	Inclusivity
3.05.07	High-dose hook effect
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3.05.10	Validation of the assay procedure
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3.06	Other studies
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3.06.05	Stability of the IVD
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PART 2: IMDRF ToC CHAPTER 4 – CLINICAL EVIDENCE	
4.02.03	Device specific clinical studies
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4.02.03c	Clinical specificity

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

IMDRF ToC Chapter heading/aspect	Testing requirements	Notes on testing requirements	Source documents
3.05.01 Stability of specimen(s)			
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); • specimen collection devices intended to be used with the IVD. • transport conditions (if applicable) (e.g., temperature and time from sample collection to arrival to the testing site); 2. Testing of a minimum of 10 specimens from different individuals (see note 3). 3. Clinical specimens shall be weakly reactive (2 to 3-x limit of detection (LOD) and include at least 1 negative sample. 4. Testing shall be conducted using 1 lot.	1. Evidence shall be provided which validates the maximum allowable time between specimen collection, processing of the specimen and its addition to the IVD. Potential transport times should be considered. 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 if extended storage is claimed in the IFU; • Stability in the extraction buffer and transport medium (if used). 3. Clinical specimens from different individuals, tested negative for NG, may be spiked with whole NG bacteria 4. Unless all specimens are expected to be processed as fresh samples within a specified time frame, the RDT performance shall be established under different storage 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 2 of this table, evidence of stability shall be demonstrated for the	

IMDRF ToC Chapter heading/aspect	Testing requirements	Notes on testing requirements	Source documents
		archiving conditions (e.g., repeated freeze/thaw cycles, temperature, duration).	
3.05.02 Validation of specimens			
Matrix effect	1. Equivalence of specimen types shall be demonstrated (see notes 1 and 2) using: a. 50 positive specimens for each claimed specimen type; b. 50 negative specimens for 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. 3. Using 1 lot of RDT and swab(s).	1. If weakly reactive clinical specimens are not available, contrived specimens generated by spiking negative specimens of each claimed type with quantified (CFU/ml or cell/mL) whole NG bacteria can be used. 2. Positive specimens (undiluted), as determined by testing with reference method, should be chosen so that the majority are near the RDT LOD. 3. Specimens of all claimed types shall be taken through the whole assay procedure from specimen collection, processing and testing. 4. The established relationship between IVD performance in claimed specimen types (e.g., cervical and vaginal 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).	CLSI EP35 [*10*]
3.05.03 Metrological traceability of calibrator and control material values			
Metrological traceability of calibrator and control values	1. The metrological traceability of the provided control material(s) to reference material shall be determined if applicable.	1. If a control material has an assigned concentration value, the metrological- (not commercial- nor documentary-) traceability to a certified reference material should be demonstrated.	PQDx_018 [*1*] ISO 17511 [*11*]

IMDRF ToC Chapter heading/aspect	Testing requirements	Notes on testing requirements	Source documents
3.05.04 Accuracy of Measurement			
3.05.04.02 Precision (Repeatability & Reproducibility)			
Repeatability and reproducibility	1. Repeatability and reproducibility (see note 1) shall be estimated using a panel of at least the following spiked specimens (see note 2 and 3): • 1 non-reactive; • 1 weakly reactive (2 to 3 x LOD or cut-off value); • 1 medium reactive (5 to 7 x LOD or cut-off value). 2. Each panel member shall be tested: • in 5 replicates per test; • over 5 days (not necessarily consecutive) with 1 run per day (alternating morning/afternoon); • in 3 different lots (see note 5 and 6) • at each of 3 different sites; • by 3 different operators 3. If a reader is required to interpret the test results, at least 3 different readers, one per site, should be used. 4. The effect of operator-to-operator variation on IVD performance shall be included as part of the precision studies (see notes 7 and 8). Testing shall be conducted: • by users representative of intended users; • unassisted; • using only those materials provided with the RDT (e.g., IFU, labels and other instructional materials). 5. Testing shall be conducted in all claimed specimen types.	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. • Users shall always be blinded to the expected results. 2. Where possible, the testing panel should be the same for all operators, lots, and sites. 3. The panel shall be prepared by spiking quantified (CFU/mL or cell/mL) representative NG reference strains into confirmed negative matrix of the claimed specimen type. 4. The whole test procedure from elution from the swab to the final result shall be utilised. • Any required accessory (i.e., swabs) included in the kit shall be used. • Swabs may be dosed with an appropriate amount of the relevant panel member. 5. Each lot shall comprise different production (or manufacturing, purification, etc.) runs of critical reagents. 6. To understand manufacturing irregularities in results obtained, at least 2 lots should be tested at each of the 3 testing sites. (3 different lots are required to be tested overall across the 3 testing sites)	CLSI EP12 [*12*]

IMDRF ToC Chapter heading/aspect	Testing requirements	Notes on testing requirements	Source documents
		7. The effect of operator-to-operator variation on IVD performance may also be considered as a human factor when designing robustness studies (see 3.06.04 Usability/human factors) 8. Operators' profiles shall be detailed in the study report (e.g., affiliation and skill level). 9. Results shall be reported as the proportion of specimens detected and in addition as graded band intensity results or numerical value (if reader is used). 10. 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. 11. Results shall be statistically analysed by ANOVA or similar methods to identify and isolate the sources and extent of any variance	
3.05.05 Analytical sensitivity			
Limit of detection (LOD)	1. The LOD of NG antigen RDTs shall be determined relative to at least two relevant/reference NG strains (see note 1). 2. The determination should comprise a minimum of 20 replicate tests of an 8-member dilution panel. 3. Testing shall be conducted using a minimum of 2 different lots (see note 5). 4. LOD shall be estimated for all the claimed specimen types (e.g., urine, vaginal or penile meatal swab).	1. Information of the NG strains used shall be provided. 2. The LOD is defined as the lowest concentration of NG bacteria (expressed in CFU/mL or cells/mL) that can be consistently detected. Typically, in > 95% of samples tested under routine clinical laboratory conditions and in a defined specimen type.	CLSI EP12 [*12*] CLSI EP17-A2 [*13*]

IMDRF ToC Chapter heading/aspect	Testing requirements	Notes on testing requirements	Source documents
	5. The entire test procedure from elution from the swab to interpretation of final result shall be utilised.	3. Determination shall be according to an established statistical method (e.g. see source document EP-12 or EP-17). 4. For qualitative assays, the logistic fit method is acceptable. 5. Each lot shall comprise different production (or manufacturing, purification, etc.) runs of critical reagents.	
3.05.05b Inclusivity	1. The capacity of NG antigen RDTs to detect clinically relevant and geographically diverse strains of NG should be demonstrated. 2. Testing of diverse NG strains (e.g., 2024 WHO reference panel) shall be conducted: • by performing two-fold end point dilution series • using 3 replicates per strain at each dilution	1. Independent of the application status, the manufacturer shall proactively scan literature and other sources for any documented mutations that might impact the safety, quality or performance of their product and notify WHO.	WHO Neisseria gonorrhoeae reference strains [*14*]
3.05.06 Analytical specificity			
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 investigated (see note 1-3) 2. Testing shall be undertaken in NG antigen reactive and non-reactive specimens (see note 5, 6), unspiked or spiked with each potentially interfering substance at the highest level found in individuals. 3. Testing shall be performed in: • 1 lot (see note 4); • 3-5 replicates; • in the relevant specimen type (see note 8);	1. The risk assessment conducted for the RDT shall identify substances/conditions for which the potential for interference can reasonably be expected with the analyte being detected in the areas of intended use and not simply rely on published data for such compounds and conditions which might be of limited relevance in resource limited settings. 2. By conducting and documenting appropriate risk assessment, testing can be performed with substances/conditions identified as likely to be significant and testing of potentially irrelevant substances/conditions avoided.	CLSI EP07-A3 [*15*] CLSI EP37-A [*16*] US FDA [*17*] ISO 14971:2019 [*18*] US FDA [*19*]

IMDRF ToC Chapter heading/aspect	Testing requirements	Notes on testing requirements	Source documents
	• at least 100 specimens total.	3. Under some circumstances stringent risk evaluation may eliminate the requirement to test some of the substances in the list but any such decision shall be documented in the submission to WHO and taken into account in the risk-benefit statements. 4. Any observed interference shall be further investigated and performance limitations of the RDT reported in the IFU. 5. 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. 6. The lot used in this study shall be the same as one of the lots in 3.05.05 LOD studies. 7. The methods and concentrations used for interference studies shall be validated so that any effect of clinical importance would be detected. 8. Interference studies should be performed with NG positive specimens with an analyte response near the LOD (not higher than 3 x LOD). The reactive specimens can be well-characterized clinical specimens or may be prepared by spiking a pool of negative specimens with a quantified (CFU/mL or cell/mL) NG reference strain. 9. For interference studies, if the technology of the test employs streptavidin, then biotin levels of up to 3500 ng/mL should be tested as part of this study.	
Endogenous and exogenous substances	1. The interference of endogenous and exogenous substances in the claimed specimen types/matrixes on the performance of the device shall be investigated. 2. A list of the interfering substances tested, and the concentrations used shall be provided. 3. The following substances expected to be found in urine shall be tested: • blood (≤ 1%); • seminal fluid; • mucus; • antibiotics; • analgesics; • over the counter deodorant sprays and powders, • hormones; • leukocytes; • albumin <1 mg/ml; • glucose; • acidic urine (pH 4.0); • alkaline urine (pH 9.0); • bilirubin. 4. The following substances expected to be found in vaginal/endocervical/penile meatal swabs shall be tested (as applicable):		

<table>
<tr><th>IMDRF ToC Chapter heading/aspect</th><th>Testing requirements</th><th>Notes on testing requirements</th><th>Source documents</th></tr>
<tr><td></td><td>• blood (≤ 60% and > 60%);
• seminal fluid;
• mucus;
• over-the-counter vaginal products and contraceptives;
• hemorrhoidal cream;
• prescription vaginal treatments;
• leukocytes (1x10^6 cells/ml);
• intravaginal hormones</td><td></td><td></td></tr>
<tr><td>3.05.06b
Cross-reactivity</td><td>1. The manufacturer shall determine the potential for false results arising from cross-reactivity with:
• Near neighbour species/strains (e.g. N. meningitidis, N. lactamica, N. polysacchareae, and N. cinerea)
• Predominant normal microbiota that may be present in each of the claimed specimen types.
• Organisms that may be present in each of the claimed specimen types.
2. Testing should include, where applicable (see notes 1-3):
<table>
<tr><td>Achromobacter xerosis</td><td>Fannyhessae vaginae</td><td>Neisseria flava</td></tr>
<tr><td>Acinetobacter calcoaceticus</td><td>Flavobacterium meningosepticum</td><td>Neisseria flavescens</td></tr>
<tr><td>Acinetobacter Iwoffi</td><td>Fusobacterium nucleatum</td><td>Neisseria lactamica</td></tr>
<tr><td>Actinomyces israelii</td><td>Gardnerella vaginalis</td><td>Neisseria mucosa</td></tr>
<tr><td>Actinomyces pyogenes</td><td>Gardnerella haemolysans</td><td>Neisseria perflava</td></tr>
</table></td><td>1. The risk assessment conducted for an IVD shall identify relevant microorganisms for which the potential for cross-reactivity can reasonably be expected for the analyte being detected and the anatomical site/s in the areas of intended use.
2. By conducting appropriate risk assessment, testing can be conducted on specimens spiked with the microorganisms identified as likely to be significant and testing of potentially irrelevant microorganisms avoided.
3. Under some circumstances stringent risk evaluation may eliminate the requirement to test some of the items in the lists but any such decision shall be documented in any submissions to WHO and taken into account in the risk-benefit statements.
4. For cross reactivity studies the organism of interest shall be tested at a high concentration (a minimum of 10^5 plaque forming units/mL for viruses and 10^6 colony forming units/mL for</td><td></td></tr>
</table>

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<tr><th>IMDRF ToC Chapter heading/aspect</th><th>Testing requirements</th><th>Notes on testing requirements</th><th>Source documents</th></tr>
<tr>
<td></td>
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<table>
<tr><td>Aerococcus viridans</td><td>Haemophilus ducreyi</td><td>Neisseria polysaccharea</td></tr>
<tr><td>Aeromonas hydrophila</td><td>Haemophilus influenzae</td><td>Neisseria sicca</td></tr>
<tr><td>Agrobacterium radiobacter</td><td>Herpes simplex virus I</td><td>Neisseria subflava</td></tr>
<tr><td>Alcaligenes faecalis</td><td>Herpes simplex virus II</td><td>Paracoccus denitrificans</td></tr>
<tr><td>Bacillus subtilis</td><td>Human papilloma virus 16</td><td>Peptostreptococcus anaerobius</td></tr>
<tr><td>Bacteriodes fragilis</td><td>Kingella dentrificans</td><td>Peptostreptococcus productus</td></tr>
<tr><td>Bacteriodes ureolyticus</td><td>Kingella kingae</td><td>Plesiomonas shigelloides</td></tr>
<tr><td>Bifidobacterium adolescentis</td><td>Klebsiella oxytoca</td><td>Prevotella spp</td></tr>
<tr><td>Bifidobacterium brevi</td><td>Klebsiella pneumoniae</td><td>Propionibacterium acnes</td></tr>
<tr><td>Branhamella catarrhalis</td><td>Lactobacillus acidophilus</td><td>Proteus mirabilis</td></tr>
<tr><td>Brevibacterium linens</td><td>Lactobacillus brevis</td><td>Proteus vulgaris</td></tr>
<tr><td>Campylobacter jejuni</td><td>Lactobacillus crispatus</td><td>Providencia stuartii</td></tr>
<tr><td>Candida albicans</td><td>Lactobacillus gasseri</td><td>Pseudomonas aeruginosa</td></tr>
<tr><td>Candida glabrata</td><td>Lactobacillus iners</td><td>Pseudomonas fluorescens</td></tr>
<tr><td>Candida parapsilosis</td><td>Lactobacillus jensenii</td><td>Pseudomonas putida</td></tr>
</table>
</td>
<td>bacteria, 10^6 cells/mL for parasites and yeasts). Contrived specimens may be used.
5. Any observed cross-reactivity shall be further investigated and performance limitations of the IVD reported in the IFU.</td>
<td></td>
</tr>
</table>

IMDRF ToC Chapter heading/aspect	Testing requirements			Notes on testing requirements	Source documents
	Candida tropicalis	*Lactobacillus lactis*	*Rahnella aquatilis*		
	Chlamydia pneumoniae	*Legionella pneumophila*	*Rhodospirillum rubrum*		
	Chromobacterium violaceum	*Leuconostoc paramensenteroides*	*Saccharomyces cerevisiae*		
	Citrobacter freundii	*Listeria monocytogenes*	*Salmonella minnesota*		
	Clostridium perfringens	*Micrococcus luteus*	*Salmonella typhimurium*		
	Corynebacterium genitalium	*Moraxella lacunata*	*Serratia marcescens*		
	Corynebacterium xerosis	*Moraxella osloensis*	*Staphylococcus saprophyticus*		
	Cryptococcus neoformans	*Morganella morganii*	*Staphylococcus aureus*		
	Cytomegalovirus	*Mycobacterium smegmatis*	*Staphylococcus epidermidis*		
	Deinococcus radiodurans	*Mycoplasma genitalium*	*Streptococcus agalactiae*		
	Derxia gummosa	*Mycoplasma hominis*	*Streptococcus bovis*		
	Eikenella corrodens	*N. meningitidis* Serogroup A	*Streptococcus mitis*		
	Enterobacter aerogenes	*N. meningitidis* Serogroup B	*Streptococcus mutans*		
	Enterobacter cloacae	*N. meningitidis* Serogroup C	*Streptococcus pneumoniae*		
	Entercoccus avium	*N. meningitidis* Serogroup D	*Streptococcus pyogenes*		

<table>
<tr><th>IMDRF ToC Chapter heading/aspect</th><th>Testing requirements</th><th>Notes on testing requirements</th><th>Source documents</th></tr>
<tr><td></td><td>
<table>
<tr><td>Entercoccus faecalis</td><td>N. meningitidis Serogroup Y</td><td>Streptococcus salivarius</td></tr>
<tr><td>Entercoccus faecium</td><td>N. meningitidis Serogroup W135</td><td>Streptococcus sanguis</td></tr>
<tr><td>Erwinia herbicola</td><td>Neisseria cinerea</td><td>Streptomyces griseinus</td></tr>
<tr><td>Erysipelothrix rhusiopathiae</td><td>Nesseria dentrificans</td><td>Trichomonas tenax</td></tr>
<tr><td>Escherichia coli</td><td>Neisseria elongata</td><td>Ureaplasma urealyticum</td></tr>
</table>
3. Samples shall be tested in triplicate.
4. Using the most relevant specimen type (e.g., urine, vaginal swab, penile meatal swab).</td><td></td><td></td></tr>
<tr><td colspan="4">3.05.07 High dose hook effect</td></tr>
<tr><td>Prozone/
High dose hook effect</td><td>1. Based on the design of the IVD, the potential for a high dose hook effect should be investigated:
• spiking negative matrix (e.g., urine, vaginal swab) with an increasing high NG bacteria concentration (at least 10^8 CFU/mL or until signal decreases)
• in 3 lots
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.</td><td></td><td></td></tr>
<tr><td colspan="4">3.05.09 Validation of Assay Cut-off</td></tr>
<tr><td>Establishment of reader cut-off</td><td>1. For RDTs provided with a reader, the way in which the reader has been designed to differentiate between</td><td>1. The statistical methods (e.g., receiver operator characteristic [ROC]) used to generate results and the testing performed to define a grey-</td><td></td></tr>
</table>

IMDRF ToC Chapter heading/aspect	Testing requirements	Notes on testing requirements	Source documents
	reactive specimens and negative specimens shall be demonstrated and described in detail.	zone/equivocal zone if applicable shall be described 2. The cut-off shall be established prior to conducting any analytical and clinical performance studies.	
3.05.10 Validation of the assay procedure			
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 an IFU commonly include the following, but the actual requirement is assay dependent and must be ascertained for each IVD: • allowable reading time (see note 2); • time interval between opening the pouch and starting the assay; • volumes, including numbers of drops; • temperatures e.g., operating temperature range, humidity. 3. Testing shall be conducted using 2 lots (1 freshly made lot and 1 lot of IVD towards the end of the assigned shelf life). 4. Specimen panel to be tested in triplicate shall be as follows (see note 3): • 1 non-reactive specimen; • 1 weakly reactive specimen (2 to 3 x LOD or cut-off value); • 1 medium reactive specimen (5 to 7 x LOD or cut-off value).	1. These parameters may be investigated as part of 3.06.04 Usability/Human factors or 3.06.05.02 In-use stability, below. 2. For RDTs where a reading interval is specified, validation data of the minimal and maximum allowable time shall be provided. 3. Pooled clinical specimens or contrived specimens (quantified NG reference strains spiked into negative matrix) shall be used.	PQDx_018 [*1*]

IMDRF ToC Chapter heading/aspect	Testing requirements	Notes on testing requirements	Source documents
	5. Studies shall be conducted in a claimed specimen type (see note 3).		
3.05.10b Validation of the control line or dot	1. The flow device shall have a control line. The nature of the control line shall be explained (see note 1).	1. The extent to which any control line corresponds to a valid test shall be validated. 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.	
3.06 Other Studies			
3.06.04 Usability/human factors			
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 weakly reactive specimen (2 to 3 x LOD or cut-off value) • 1 medium reactive specimen (5 to 7 x LOD or cut-off value). 3. The influence of the following factors on expected results (both reactive and non-reactive) shall be considered	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 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 low- and middle-income countries so that the limitations of the device can be understood. For example temperature and relative humidity (RH) ranges that exceed those of claimed operating conditions and which could cause test failure (incorrect/invalid results)	ISO 14971:2019 [*18*] US FDA [*19*] IEC 62366-1:2015 [*20*]

IMDRF ToC Chapter heading/aspect	Testing requirements	Notes on testing requirements	Source documents
	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 including sampling procedure and different swab types (for products that do not include the swab); • specimen processing; • timing of processing steps; • specimen volume including number of drops; • reagent volume provided and used; • specimen dilution/concentration factor; • reading time; • operating temperature, pressure, and humidity. 4. Ruggedness shall be considered based on the risk-assessment conducted, for example but not limited to the following conditions: • RDT sturdiness including robustness of packaging and labelling. RDT in final packaging shall be subjected to drop-shock testing; • permanence of component labels: print legibility, adhesiveness (see notes 4, 5); • effects of lighting and humidity (see note 5); • placement of the test device on non-level surface; • the effect of moving the test device while it is running (e.g., relocating to another surface or dropping it).	should be considered (e.g., temperature up to 40°- 45°C and RH between 5-95%). 3. 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). 4. The resilience of label (e.g., strength of attachment, print stability, legibility over time, damp tolerance) shall be evaluated. 5. The impact of lighting: • on the visual reading of the control and test lines. • on labelling (fading); 6. 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. 7. Some of these parameters/factors may be investigated as part of 3.05.10a Validation of assay parameters or 3.06.05.02 In-use stability. 8. For the purposes of this document, ruggedness means the ability to resist environmental shocks of a variety of kinds. 9. Pooled clinical specimens or contrived specimens (quantified NG refence strains spiked into negative matrix) shall be used.	

IMDRF ToC Chapter heading/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); • impact of dust and mould on componentry (e.g., optics if applicable). 6. Studies shall be conducted in a claimed specimen type (see note 9).		
3.06.04b Usability: 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; • proper test procedure; • proper reader procedure (if included); • 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 including those whose native language may not be the language of the IFU if necessary; • in their usual working environment, not employees of the manufacturer.	1. Instructions for use and labelling shall be clear and easy to understand; use of pictorial instructional material is encouraged. If additional resources such as videos are provided, the information provided in the videos shall be the same as the information provided in the IFU. 2. Requirements listed may be investigated as a separate study or included as part of the results interpretation study and/or clinical study. 3. Testing may be conducted using questionnaire-based surveys.	IEC 62366-1:2015 [*20*]
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:	1. The contrived tests shall be prepared by persons different from those reading the results. The tests shall be randomized prior to the users reading the results.	

IMDRF ToC Chapter heading/aspect	Testing requirements	Notes on testing requirements	Source documents
	• non-reactive; • range of invalid results; • reactive; • weakly reactive. 3. Testing subjects shall consist of: • at least 15 intended users, including those whose native language may not be the IFU language; • in their usual working environment, not employees of the manufacturer.		
3.06.05 Stability of the IVD			
3.06.05.01 Claimed Shelf-life & 3.06.05.03 Shipping stability	1. Real time stability studies shall be conducted on a minimum of 3 lots of final design product (see note 1), using the conditions expected in the environment of intended use. 2. Lots shall be subjected to simulated "transport stress" before real time studies are undertaken on these lots: • the effects of this simulated "transport stress" (i.e., extreme temperature, humidity and pressure conditions) shall be documented separately and in addition to the real time studies. 3. Real time shelf-life studies shall evaluate the storage temperature and humidity range. 4. IVD in final packaging shall be subjected to simulated physical stress conditions (e.g. drop-shock, inversion, vibration, physical handling and stacking). 5. Testing in triplicate shall be undertaken using a panel of specimens of at least: • 1 non-reactive specimen;	1. The lots used shall be manufactured to validated scale according to finalised protocols, including packaging, labelling, quality assurance and quality control specifications and IFU method: • each lot shall comprise different production (or manufacturing, purification, etc.) runs of critical reagents and ideally some of the reagents should be near the end of their assigned shelf lives; • the lot numbers of critical reagents and kit components in each lot of RDT shall be documented and reported. 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, open container, in-use) shall be obtained on all variants, even if the contents of the containers are identical.	TGS-2 [*21*] Annex to TGS-2 [*22*] ISO 23640:2011 [*23*] CLSI EP25 [*24*] ASTM D4169-22 [*25*]

IMDRF ToC Chapter heading/aspect	Testing requirements	Notes on testing requirements	Source documents
	• 1 weakly reactive specimen (2 to 3 x LOD or cut-off value); • 1 medium reactive specimen (5 to 7 x LOD or cut-off value). 6. The most challenging specimen type shall be used. 7. In addition, to address specificity a minimum of 100 negative specimens shall be tested at T=0 and at the end of the claimed shelf life. 8. Stability of labelling shall be determined (see chapter 3.06.04).	3. Flow time and time to band development should be reported. 4. The number 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 shall not replace the need for real time studies. 7. Contrived positive specimens (quantified NG reference strain spiked into negative matrix) are the preferred specimen type but with justification, clinical specimens may be used.	
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 (see note 1). 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 in at least 1 lot. 5. Testing in triplicate shall be undertaken using a panel of specimens of at least: • 1 non-reactive specimen; • 1 weakly reactive specimen (2 to 3 x LOD or cut-off value);	1. In-use stability of labile components shall be conducted using components in their final configuration.	

IMDRF ToC Chapter heading/aspect	Testing requirements	Notes on testing requirements	Source documents
	• 1 medium reactive specimen (5 to7 x LOD or cut-off value). 6. The most challenging specimen type shall be used.		

Part 2: IMDRF ToC Chapter 4: Clinical evidence

IMDRF ToC Chapter heading/aspect	Testing requirements	Notes on testing requirements	Source documents
4.02.03 Device specific clinical studies			
4.02.03a General requirements for clinical performance studies	1. Clinical performance characteristics 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: • by the intended users representing relevant intended use settings (see note 1); • on specimens collected from all sections of the population for which claims are made (note 2); • using specimens from intended use populations in different geographical settings (minimum of 3 settings in more than 1 WHO region including LMICs) (see note 3); • on all claimed specimen types; • using at least 2 lots at each testing site (see note 4). 3. The reference method shall include (a) state of the art NAT(s) that detect(s) NG (two different target sequences) (see notes 5 to 7). 4. Culture may be used in addition to NAT testing, but cannot replace it. 5. Reference testing shall be conducted using first catch male urine and vaginal swabs. 6. Discrepant, invalid, and unexpected results shall be further evaluated (see notes 8 to 11). 7. The procedure for selection of study subjects/specimens, how these represent an intended	1. RDTs for NG antigen detection are generally used by laboratory professional or by healthcare workers/lay providers trained on the use of the IVD in resource limited and primary care settings. This should be considered when preparing evaluation protocols. 2. The inclusion and exclusion criteria shall be clearly stated 3. The 3 settings chosen shall reflect the intended use healthcare settings. 4. Approximately half of the specimens shall be tested on different lots at each site 5. The method and specimen types used for molecular testing shall be specified. 6. Estimates of clinical sensitivity and specificity to the reference method shall be reported with 95% confidence intervals 7. Clinical performance shall be stratified by gender, symptom status (symptomatic vs. asymptomatic), and specimen type. 8. Discrepant results shall be resolved as much as possible (e.g., by performing gram staining of urethral swabs from symptomatic men), however performance characteristics shall be based on the original result.	

IMDRF ToC Chapter heading/aspect	Testing requirements	Notes on testing requirements	Source documents
	use population and how bias has been addressed shall be clearly described (see notes 2 and 3).	9. Problematic specimens including those with unexpected results, but which otherwise meet selection criteria for the study, shall not be excluded from analysis. 10. Inconclusive results shall not be excluded from the denominator data for analysis. 11. All invalid test results shall be recorded and analysed separately in the final performance calculation. 12. Up to 25% of the clinical specimens may be well-characterised archived specimens if the impact of storage/freezing has been validated (see 3.05.01). 13. The following basic information shall accompany each subject/specimen at a minimum: • asymptomatic or symptomatic • type of symptom • treatment status • gender • specimen type • collection method and material • professionally-collected or self-collected • product name, manufacturer and product code of the reference test used	
4.02.03b Clinical sensitivity	1. A minimum of 200 prospective NG positive specimens collected from different symptomatic and asymptomatic subjects shall be tested per each claimed specimen type (see note 12). 2. If self-collection is claimed, 50 prospective NG positive specimens shall be collected/tested per applicable specimen type and compared to specimens collected from the same individuals by the health care provider.		
4.02.03c Clinical specificity	1. Testing of at least 400 confirmed NG-negative specimens per specimen type from symptomatic individuals shall be tested.		

F. Source documents

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