Medicines & Healthcare products Regulatory Agency

MHRA

TARGET PRODUCT PROFILE

Laboratory-Based SARS-CoV-2 Viral Detection Tests

Version Control

Version	Date Issued	Description
1.0		Initial document
2.0	10/11021	Changes to Clinical Sensitivity and Limits of Detection to accommodate assays with additional benefits, including: multiplex, short turn around times or high throughput. Increased Clinical Specificity in line with the changing state of the art and continuous quality improvement. Updated regulatory sections in line with the UK departure from the EU Updated intended-use and included statements concerning SARS-CoV-2 variants of concern Updated sections on Reference Standard and Sample types. Harmonised introductory sections and Annex's with newer TPP formatting Included considerations of clinical performance evaluation, clinical impact, downstream sequencing and carry over Removed requirements considering supply volumes, equipment size, sample volume

The purpose of a Target Product Profile "TPP"

MHRA Target Product Profiles (TPP) are guidance documents which aim to support and accelerate the development and evaluation of new medical technologies to address specific unmet clinical or public health needs of high strategic priority to the UK population.

TPPs summarise the key features and anticipated performance specifications of a new device in advance, to enable innovators to design and develop high quality products that are fit for purpose and meet specific health-related goals. They are intended to be used to support product design, research and development planning and to facilitate discussions with regulators.

MHRA TPP's are aspirational documents aimed at test manufacturers and are based upon the best available evidence and independent expert opinion. They do not represent UK government policy and are not regulatory requirements. For information on the current National technical validation process and their relevant performance goals, please see National technical validation process for manufacturers of SARS-CoV-2 (COVID-19) tests - GOV.UK (www.gov.uk)

MHRA TPPs are living documents that are reviewed on a frequent basis, dependent on the specific disease area, and updated as additional evidence and information becomes available. Manufacturers should ensure they are working to the most recent version of a TPP.

Intended use for this TPP

This TPP is intended to be used by manufacturers to support the development of laboratory-based in vitro diagnostic tests for detection of current SARS-CoV-2 infection in people with and without symptoms., as part of UK government national testing programmes or accredited private testing services.

The exact performance requirements will vary depending on the specific use-case, taking into consideration the following:

1. The target population (e.g. Children, young people, adults, older people)
2. The setting (e.g. A&E, testing centres, workplaces)
3. The intervention decision being informed (e.g. release from isolation, contact tracing, infection control measures etc).

This TPP does not consider tests for use in the following possible scenarios:

- Self-Tests for use at home
- Point of care tests to be performed by a professional (see here for full definitions) in a health and/or social care setting.
- Prognose a patient's likely outcome, including disease severity or survival.
- Predict or monitor a patient's likely response to treatment.

Clinical performance requirements

The TPP sets out the requirements based on the consensus of what is “desired” and minimally “acceptable” in the opinion of healthcare professionals and scientists given the current situation. Products meeting the “desirable” criteria will likely have a role in a greater number of use-cases than products that only meet the “acceptable” criteria.

The decision to use a particular test for a specific use must be informed by clinical expert opinion at the time, considering the disease prevalence, risks, benefits and downstream consequences of testing vs not-testing. **Annex 2 provides tables and further discussion which may be useful in supporting decision making, by demonstrating the impact of changing sensitivity, specificity and prevalence on the numbers of false positives and negatives.**

Future developments

These profiles are subject to review and change, as we gain a greater knowledge of the virus, the disease and our needs for an effective response. They may need to be updated at short notice.

As our knowledge and understanding of the disease changes and the UK clinical needs change, so will the specifications. A test that meets this version of the TPP may not meet future versions.

Key to Table

Desired: Highly desirable features of considerable benefit. As time is of the essence, if omitting one of these features significantly accelerates development and production it can be considered.

Acceptable: Defines the minimum acceptable feature.

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TARGET PRODUCT PROFILE
COVID-19
Laboratory-based SARS-CoV-2 Viral detection testing

Key feature	Desired	Acceptable	Comment
SCOPE			
Intended Function (s)	Used in the detection of current SARS-CoV-2 infection And Differentiation from recent or recovered infection. And/or Differentiation of SARS-CoV-2 from other respiratory infections. And/or Differentiation of SARS-CoV-2 Variants of Concern (VoCs)	Used in the detection of current SARS-CoV-2 infection	**Current infection**: an infection in which the causative organism has the potential, either now or in the future, to cause disease or onward transmission. An individual with a current infection may not display disease symptoms, require treatment or be infectious at the time of testing. Manufacturers should indicate if the test is only intended for use in a specific population or setting and would be expected to justify the balance between risk and benefits. Tests with “acceptable” levels of sensitivity and specificity may only have application in a limited number of use-cases and will likely require additional risk mitigation measures, such as confirmatory testing or infection control. Refer to Annex 2.

			Whilst multiplexing is desirable for specific use-cases, it may not be appropriate for all.
Target population	Adults and children with or without symptoms		Populations “without symptoms” represents a range of pre-symptomatic, peri-symptomatic, sub-symptomatic and truly asymptomatic phenotypes, spanning all stages of disease (early and late) and a wide range of viral loads (low to high). Manufacturers should carefully consider the design features of tests intended for use in children to ensure their safe and effective operation and acceptability. Manufacturers should ensure that risk-management and clinical performance is appropriate for their claimed target populations. Evidence of clinical performance should be provided for each population claimed by the manufacturer and performed by the relevant user group. As the immune status of the UK population changes over time, manufacturers should understake studies to evaluate how the test continues to perform in vaccinated and re-infected individuals.

Target user	Trained healthcare / public health professionals (i.e. one of the 10 health and social care professional bodies that are overseen by the professional standards authority) and suitably trained and assessed as competent lab technicians or scientists.	A target user will perform the assay, interpret and communicate the results. Full training appropriate to the intended user is required.
Target use Setting	Healthcare and Medical Laboratories	These exclude Point of Care (POC) testing environments which will utilise tests types that are appropriate for that setting. Includes both private and public sector laboratories.
TEST DESIGN CHARACTERISTICS		
Test format	A standardised kit that contains all materials required for the laboratory procedure that includes controls, reagents and Instruction for Use (IFU). All equipment and accessories needed to perform the assay and sample processing included, with the exception of routine laboratory consumables such as pipettes, pipette tips, disinfectants, screw cap eppendorfs, heat blocks, fluorescent readers etc. Should the technology not be compatible with routinely used sample collection devices these should also be provided at the same time as the test kit.	May apply to, for example: • Open and Closed high throughput platforms • Microarray testing (for broad range pathogen testing) All accessories need to be validated for use in combination with the test as part of the CE, CE UKNI or UKCA marking. Specifications for general reagents that can be used with open or closed systems must be clearly defined.

Target Analyte (Measurand)	Dual (or more) SARS-CoV-2 targets (e.g. nucleic acid(s), antigen(s) or other targets) Single (or more) targets for a range of infectious respiratory viruses, including influenza A virus, and influenza B virus, RSV A & B Single (or more) targets for all current SARS-CoV-2 variants of concern	Single SARS-CoV-2 target (e.g. nucleic acid, antigen or other target)	Evidence demonstrating the association of the analyte(s) with current SARS-CoV-2 infection (scientific validity) should be provided. Manufacturers should consider targeting assays to conserved regions/epitopes of SARS-CoV-2 to ensure the detection of current and future variants Dual antigen targets could include multiple epitopes for the same protein. Multiplex sytems must be able to clearly distinguish between targets included in the panel. Assays that detect whole SARS-CoV-2 Virus may also be acceptable There is a requirement on suppliers to confirm performance in detection of both current and emerging strain variants of SARS-CoV-2 as they arise and confirm this to MHRA where VOC (variants of concern) or VUI (variants under investigation) are reported in line with MHRA requirements, see Annex 1
Sample type	Method not requiring a swab (e.g. saliva, sputum, stool, breath sample)	Nasal and/or throat swab	All sample types claimed as appropriate in the instructions for use must be validated as part of the performance

	Validation of assays for use with respiratory tract samples' (sputum, endotracheal, bronchoalveolar lavage, nasopharyngeal aspirate), tissue samples or cerebral spinal fluid may also be desirable for some specific use cases.		assessment. Study sample sizes for each sample type must be sufficiently powered. Methods not using invasive swabs are desirable due to the individual's discomfort and pre-analytical errors. They may also facilitate improved quantification of viral load. Manufacturers should ensure that swabs are appropriate for the intended population (i.e. smaller swabs for children).Consideration should be given to compatability of sample with collection media/buffers and assay performance Not all sample collection buffers or methods are compatible with downstream testing requirements e.g. genotyping and sequencing.
Compatible sample collection	Test is validated for use with the sample types listed above which may be collected into a variety of sample collection medias e.g. viral transport medium, inactivation medium, solvents, dry swabs, and saline in addtional to media provided with the kit.	Test is validated for use with sample types above, which may be collected into a media provided with the kit.	Additional processing or re-sampling may be required if the availability of quality RNA for downstream processing cannot be met by any single test method

	Sample media is suitable for downstream processing including sequencing for identification of lineage, mutations and variants of concern		
Result output	Semi-Quantitative	Qualitative	Whilst it is desirable for analytical methods to be quantitative, the nature of swab sample collection means that results are likely to only be semi-quantitative. For semi-quantitative assays, an appropriate number of calibration points and replicates covering the range of reliable signal should be applied. Qualitative results may not support all downstream applications (e.g sequencing).
Power requirement	Standard mains power suply with UPS and the capability for battery power.	Mains power supply	
Internal controls	Whole process positive controls, negative controls, internal and external controls are required to confirm validity of end-end processing and clearly	Should include positive controls and negative controls with option to include internal controls/external controls in a single or multiplex format.	Invalid results may be due to sampling technique, the presence of biological inhibitors or matrix effects. .

	identifiy sample inadequacy results as invalid.		
Technical failure rate	Less than 0.2%	Less than 1%	In use failures resulting from mechanical, controls, calibration or other factors which may not be regarded as reportable as an adverse event under the UK Medical Devices Regulations 2002 (SI 2002 No 618, as amended) (UK MDR 2002). Does not include failure due to sample collection or technical issues outside of scope of test (e.g house-keeping genes)
Ease of use and result interpretation	Suitable for target user groups (i.e trained healthcare professionals)		
Need for calibration	No calibration required	Remote or auto-calibration	
Identification capability	Unique barcode or equivalent for integration into electronic systems	Labelling of the device with the subjects identification must be feasible	
Carry Over	Bioinformatics approaches used to detect human-human sample contamination to monitor carryover.		The risk of carryover should be evaluated at each step of the assay.
PERFORMANCE CHARACTERISTICS			
Clinical (diagnostic) sensitivity (or Positive Percent Agreement)	Greater than 99% (with 95% two-sided confidence interval entirely above 97%).	Greater than 80% (with 95% two-sided confidence interval entirely above 70%).	At least **150** positive cases (per sample type). Greater sample numbers will be required to support higher performance claims.

			Multiplex assays and assays with shorter turn-around-times or greater throughput may justify the lower 80% sensitivity requirement, in specific use cases. However, standard RNA extraction based RT-PCR assays should be achieving the Desirable performance.
Clinical (diagnostic) specificity (or Negative Percent Agreement)	Greater than 99% (with 95% two-sided confidence interval entirely above 97%).	Greater than 97% (with 95% two-sided confidence interval entirely above 93%).	A minimum of **250** COVID-19 negative cases (per sample type). Testing should include all claimed specimen types and provide details of collection device and transport medium that have been validated for use with the assay.
Clinical Performance Evaluation	Positive and negative cases should be recruited prospectively and consecutively or randomly from the target population without prior knowledge of their disease status (e.g. single-gate design).	When prevalence is low, or in emergency use situations (e.g. a surge in cases of a new variant of Concern (VoC)), case-control designs using clinical samples with viral load distributions (determined by PCR) generalisable to the target population may be necessary.	Two-gated case-control designs can introduce selection and spectrum bias and should be avoided if possible, refer to Rutjes, 2005. Claims made using such approaches (minimum criteria) are likely to overestimate the Clinical Performance. Testing of all claimed specimen types should be performed with sufficient power, and details provided for collection

	Studies directly comparing a new assay to the current state of the art test would be advantageous. Test samples should be collected in the target setting at the same time as samples for the reference standard and any comparator methods. In some cases the type of test or order of testing may need to be randomised. Alternative study designs looking at the impact of using tests on disease spread (for tests to rule-in) or outbreaks (for tests to rule-out) should also be considered.	Once in clinical use, manufacturers should immediately start to collect and make available in a timely way "Desirable" clinical performance evidence from post-market surveillance studies	devices and transport media that have been validated for use with the assay. Practical recommendations for designing diagnostic accuracy studies in low prevalence settings can be found in Holtman, 2020. Further information on the design and conduct of clinical performance evaluations of SARs-CoV-2 tests can be found in Doust, 2021 Reporting of clinical performance evaluation studies should be in line with STARD 2015. Results should include a diagram of participant flow, participant clinical and demographic characteristics including distibutions of disease severity/stage and alternative diagnoses, time intervals between index and reference tests,and a 2x2 table of results in addition to the measures of diagnostic performance with 95% confidence intervals. All efforts should be made to establish the disease/infection status of a study participant. E.g. evidence of prior infection (describing test results and

			timing) and vaccination status (date of vaccination/s, vaccine).
Clinical Reference Standard	A composite clinical reference standard, against which the clinical sensitivity and specificity are calculated. This could, if scientifically valid and appropriate for the defined context of use, include considerations of immunity status, disease phase, virus characteristics, and infectivity.	A validated CE, CE UKNI or UKCA marked RNA extracted RT-PCR laboratory method in current clinical use that itself performs within the desirable analytical and clinical performance specifications of this TPP, against which the Negative/Positive Percent Agreement is calculated.	See the NICE evidence standards framework for more information on composite clinical reference standards. https://www.nice.org.uk/Media/Default/About/what-we-do/covid-19/Diagnostic-tests-for-COVID-19-evidence-standards-framework.pdf An example of a temporary Composite Reference Standard for COVID19 can be found here https://www.cebm.net/covid-19/a-composite-reference-standard-for-covid-19-diagnostic-accuracy-studies-a-roadmap/. For samples with discordant results further testing could be done to try and explain the direction of discordance (for example, repeating the sample run on both tests or using a third method, if available). But this should not influence claims of sensitivity and specificity.
Analytical specificity	No clinically relevant cross reactivity or interference to all organisms and agents listed in Annex 1.	No clinically relevant cross reactivity to common seasonal respiratory pathogens. Minimal interference caused by common interferents at clinically relevant concentrations	Manufacturers should consider inclusivity, exclusivity, cross-reactions and exogenous/endogenous interference. See annex 1 for list

	Inclusive of all SARS-CoV-2 variants of concern. Demonstrated in silico and in vitro, where suitable reference materials are available.	(dependant on sample type and analyte) Inclusive of SARS-CoV-2 variants of concern. Demonstrated in silico and in vitro, where suitable reference materials are available.	In silico analyses including database searches should be performed to confirm the species specificity, avoiding the possibility of accidental cross reaction with human and bacteria.
Limit of Detection (LOD)	An appropriate unit of measurement for the target analyte (e.g. International Units) equivalent to a viral load of less than 100 SARS-CoV-2 RNA copies/mL of sample. Standard RNA extraction based RT-PCR assays should be achieving the Desirable LoD performance.	An appropriate unit of measurement for the target analyte (e.g. International Units) equivalent to a viral load of less than 10,000 SARS-CoV-2 RNA copies/mL of sample. Multiplex assays and assays with shorter turn-around-times or greater throughput may justify the acceptable LoD performance.	The LoD is the lowest concentration of analyte that can be consistently detected in ≥95% of samples tested under routine laboratory conditions and in the appropriate sample matrix. This concentration must yield an assay value that can be reproducibly distinguished from values obtained with samples that do not contain the analyte. Refer to appropriate standards (e.g. CLSI EP17) in the design of studies. Ideally multiple batches/lots of kits/reagents should be used when establishing the LoD. Where an appropriate International Standard, reference material or reference measurement procedure is available for the analyte(s) this should be used. For examples, see here. If there are no comparative reference materials or measurement procedures available, evidence should be provided to demonstrate the choice of strategy for determining LOD is appropriate.

			To demonstrate equivalence of the analyte(s) with viral load in copies/mL, the quantity value and measurement uncertainty of the clinical samples used should be assigned using an appropriate reference method (e.g. dPCR). Commercially available quality control materials may not be value assigned with sufficeint accuracy to enable LoD evaluation. The evaluation of LoD for some analytes using samples characterised in terms of RNA copies/mL may not be optimal and different criteria may need to be considered, if accompanied by sufficient evidence of scientific validity.
Clinical impact	Evidence that the test improves system and/or an individual's outcomes (for example, time to diagnosis, subjects experience, use of pre-cautionary COVID-19 isolation facilities). Evidence that the test provides good value.		Refer to NICE evidence standards for further information https://www.nice.org.uk/Media/Default/About/what-we-do/covid-19/Diagnostic-tests-for-COVID-19-evidence-standards-framework.pdf The purchase price/cost of a test alone may not be a good indicator of its valueNICE use the incremental cost effectiveness ratio (ICER) as their preferred measure of value. Whilst NICE do not have a

			fixed threshold for cost-effectiveness, technologies exceeding £30,000/QALY have a higher probability of rejection and need to identify a strong case with regards to the certainty of evidence and innovative nature of the technology.
Turnaround time	Less than 90 minutes from sample to result	Less than five hours from sample to result	The time is from reciept of sample in test laboratory.
Throughput	More than 200 tests per machine/module every 4 hours	More than 300 tests per machine/module every 24 hours	
TEST PROCEDURE CHARACTERISTICS			
Hands on time	Less than five minutes per sample	Less than 20 minutes per sample	
Sample processing and handling	Standardised sample-processing steps, using medical laboratory equipment (centrifuge, vortex, pipette etc).		
Biosafety	Buffers or other components provided with kit or sample collection devices are proven to inactivate SARS-CoV-2 and any other respiratory viruses in scope of assay enabling entire process to be carried at CL2.	Requires inactivation pre-step at CL3 or CL2+. Remaining steps can be preformed at CL2.	Systems specifying need for lower biosafety environments must demonstrate sample inactivation and virus containment. Instructions for use must confirm biosafety requirements for sample handling and inactivation evidence Appropriate consideration should be given for biosafety in the environment which the test should be carried out

Risk in use	Risks have been managed according to ISO 14971		
OPERATIONAL CHARACTERISTICS			
Test kit storage and stability conditions	No cold chain (15 to 30 °C)	Storage of kit and reagents at -20°C and above for at least 12 months. Stable for 3 hours once removed from cold storage.	Packaging to be as compact as possible to facilate storage. Must be made clear if reagents can withstand freeze and thaw and will not be detrimental to the assay
Assay end point stability (time window during which signal remains valid)	up to 1 hour	up to 30 minutes	
Operating conditions	15 to 30 °C		
Connectivity	Wireless and cable connectivity via LIMS systems	Cable connectivity via LIMS system	Results may need to be transferred by digital media e.g. CSV files
Presentation of results	Easy to capture for interpretation and able to record public health data Results do not require post run analysis (automatically called). Ability to access raw data e.g. RT-qPCR/RT-LAMP fluorescence traces	Easy to capture for interpretation and able to record public health data	Integrity of data must be maintained
Reproducibility	More than 95% between repeats at LoD More than 99% at higher concentrations		Manufacturers should consider ISO 20395:2019 and ISO 5725-1 when evaluating reproducibility.
Disposal requirements	No additional disposal requirements beyond normal laboratory practice. Any special containment or disposal requirements need		

	to be clearly specified (e.g. contamination control for RT-LAMP post amplification products).		
Training needs (Time dedicated to training session for end users)	Less then half day training needed for for laboratory staff	Less than one day of training needed	
OTHER			
Label and Instructions for Use	Conforms to UK MDR 2002 and relevant designated standards		
Regulatory status	CE, CE UKNI or UKCA marked	Exempt according to Regulation 12 of the UK MDR 2002.	For further information on the regulation of medical devices on the UK market, please see our guidance. Specific guidence for manufacturers of COVID tests can be found here
Maintenance	Preventive maintenance should not be needed until after 2 years or 100,000 samples. An alert should be included to indicate when maintenance is needed.	Preventive maintenance should not be needed until after 1 year or 10,000 samples; an alert should be included to indicate when maintenance is needed.	Assuming the equipment is used at capacity 24 hours a day, seven days a week
Design and manufacturing environment	ISO 13485:2016		

ANNEX 1: ASSAY VALIDATION

Establishing Performance Characteristics.

It is recommended that the following aspects are considered when designing and validating the assay. Analytical performance evaluations should test any multiplex molecular test system in its final configuration, and not in separate singleplex experiments.

- Reference material should be used to establish performance, including standard validation panels, quality control materials and proficiency testing materials
- When establishing the performance of the test, manufacturers must consider the analytical sensitivity and specificity of the test to SARS-CoV-2 Variants Under Investigation (VUI) and of Concern (VOC) , including-those listed on gov.uk by Public Health England). A full up to date list of variants can be found at https://www.gisaid.org/. Manufacturers are expected to routinely perform in silico analysis of listed VOC and VUI of gov.uk as a standard post market surveillance analysis. Where an assay is suspected or known to be affected by a listed VOC OR VUI, the manufacturer should inform MHRA within 48 hours of discovery.
- When establishing analytical specificity, the following should be considered:
    - Samples from patients who have received any licenced vaccine at several time points post vaccination (e.g. <5 days and 1-6 months).
    - prepandemic samples,
    - other coronavirus, SARS-CoV-1,
    - MERS- coronavirus
    - hCoV 229E, OC43, HKU1, NL63
    - Adenovirus (e.g. C1 Ad. 71)
    - Human Metapneumovirus (hMPV)
    - Parainfluenza virus 1-4
    - Influenza A & B
    - Enterovirus (e.g. EV68)
    - Respiratory syncytial virus
    - Rhinovirus
    - *Chlamydia pneumoniae*
    - *Haemophilus influenzae*
    - *Legionella pneumophila*
    - *Mycobacterium tuberculosis*
    - *Streptococcus pneumoniae*
    - *Streptococcus pyogenes*
    - *Bordetella pertussis*
    - *Mycoplasma pneumoniae*
    - *Pneumocystis jirovecii (PJP)*

- Potential interferents may originate from the following endogenous and exogenous sources and may be more relevant to ligand-binding based antigen tests than

conventional PCR based assays. Manufacturers should declare if any other endogenous/ exogenous substances will impact the assay.

- Antibacterial, systemic
- Antibiotic, nasal ointment
- Anti-viral drugs
- Antibodies developed against protein expression system used to generate recombinant antigens
- Bilirubin
- Biotin
- Blood (human)
- Haemoglobin
- Human Anti-mouse Antibody (HAMA)
- Medications most often prescribed in the population for which the test is ordered
- Mucin: bovine submaxillary gland, type I-S
- Nasal sprays or drops
- Nasal corticosteroids
- Nasal gel
- Protein
- Rheumatoid Factor
- Throat lozenges, oral anaesthetic and analgesic
- Triglycerides

In addition the assay must deliver across the cinical range of haematocrit values

Post Market Performance considerations

An increase in the number of cases with new SARS-CoV-2 variants has been observed in the United Kingdom. MHRA is aware that some laboratories have reported poor performance of some diagnostic assays that include an S-gene target. Such impact on test performance may be linked to the virus variant alpha or other variants. Mutations are not exclusive to the S-gene and action is required by manufacturers regardless of the diagnostic assay targets.

In line with UK MDR 2002 vigilance and field safety corrective action reporting requirements, MHRA consider reports relating to Variants of Concern (VOC) to be serious public health threats, therefore significant safety issues should be reported within 48h.

Actions specific to new VOCs:

1. Inform MHRA of the outcome of your initial risk assessment on the performance of your assay in light of identified variants of concern and your plan to mitigate against any new risks from mutations, including your timelines for addressing these.
2. If the performance of your assay is directly impacted by new virus variant(s), a Field Safety Notice should be issued immediately to alert customers.

3. A Post Market Surveillance plan (PMSP) should be in place to continuously monitor, investigate and assess newly emerging variants of SARS-CoV-2. The PMSP can include:

a. Fortnightly in silico checks of assay targets against GISAID sequence databases (https://www.gisaid.org) [*Please note that high profile potential issues should be immediately investigated]
b. Scientific literature and post market intelligence gathering
c. Outcomes of EQA schemes when available
d. Use of reference materials when available
e. Reporting potential safety issues of any new clinically significant variant SARS-CoV-2 strain on the performance of your assay to MHRA

Public Visibility of device assurance

MHRA intend to publish safety actions resulting from manufacturer in silico analysis and in vitro testing against variants of concern. The manufacturer should request if specific submitted information should not be made public. Public access to test device assurance will mutually benefit commercial suppliers and test device users.

Annex 2: Diagnostic accuracy considerations

When considering procurement and deployment of devices for any given clinical use-case, it is recommended to consider the maximum number of false positives and false negatives (Table 1) that would be acceptable for the new test based on the possible consequences of these misdiagnoses. It is also helpful to consider the post-test probability that someone with a positive or negative result has infection (Table 2). Programmes and testing services deploying self-tests into routine use should consider such information when determining where and when testing may be clinically/cost-effective and acceptable to end users.

Table 1: The tables below presents the numbers of false positives and negatives in a cohort of fixed size (1,000,000) with varying prevalence of SARS-CoV-2 infection.

	Numbers per	1000000 tested					
		Prevalence	**20.0%**				
		SENSITIVITY					
			99.0%	97.0%	95%	80%	
SPECIFICITY		**Test Result**					
	99.0%	False Positives	8000	8000	8000	8000	
		False Negatives	2000	6000	10000	40000	
	95.0%	False Positives	40000	40000	40000	40000	
		False Negatives	2000	6000	10000	40000	

	Numbers per	1000000 tested					
		Prevalence	**5.0%**				
		SENSITIVITY					
			99.0%	97.0%	95%	80%	
SPECIFICITY		**Test Result**					
	99.0%	False Positives	9500	9500	9500	9500	
		False Negatives	500	1500	2500	10000	
	95.0%	False Positives	47500	47500	47500	47500	
		False Negatives	500	1500	2500	10000	

	Numbers per	1000000	tested				
		Prevalence	**1.0%**				
		SENSITIVITY					
			99.0%	97.0%	95%	80%	
SPECIFICITY		**Test Result**					
		False Positives	9900	9900	9900	9900	
	99.0%	False Negatives	100	300	500	2000	
		False Positives	49500	49500	49500	49500	
	95.0%	False Negatives	100	300	500	2000	

	Numbers per	1000000	tested				
		Prevalence	**0.2%**				
		SENSITIVITY					
			99.0%	97.0%	95%	80%	
SPECIFICITY		**Test Result**					
		False Positives	9980	9980	9980	9980	
	99.0%	False Negatives	20	60	100	400	
		False Positives	49900	49900	49900	49900	
	95.0%	False Negatives	20	60	100	400	

Table 2: The following tables show the post-test probability of having an infection as the prevalence (or pre-test probability) changes. The percentage of people testing positive who are infected (Positive Predictive Value)) and the percentage of people testing negative who are infected (1-Negative Predictive Value) are shown for different prevalences from 0.2% to 20% (1 in 500 to 1 in 5). Programmes and testing services should determine their own acceptance criteria.

Desirable Test

Sensitivty	9%						
Specificity	99%						
Prevalence		***0.20%***	***0.50%***	***1.00%***	***2.00%***	***5.00%***	***10.00%***	***20.00%***
% +ves infected (PPV)		16.56%	33.22%	50.00%	66.89%	83.90%	91.67%	96.12%
% -ves infected (1-NPV)		0.0020%	0.0051%	0.0101%	0.0202%	0.0505%	0.1009%	0.2016%

Acceptable Test

Sensitivty	80%

Specificity	95%						
Prevalence	***0.20%***	***0.50%***	***1.00%***	***2.00%***	***5.00%***	***10.00%***	***20.00%***
% +ves infected (PPV)	3.11%	7.44%	13.91%	24.62%	45.71%	64.00%	80.00%
% -ves infected (1-NPV)	0.042%	0.105%	0.210%	0.4193%	1.0417%	2.0619%	4.0404%

ANNEX 3 Glossary

BSL	Biological Safety Level
CL	Containment level
dPCR	Digital polymerase chain reaction
IVD	In Vitro Diagnostic
LAMP	Loop-mediated isothermal amplification
LIMS	Laboratory Information Management System
LoD	Limit of Detection
NAT	Nucleic acid testing
PCR	Polymerase chain reaction
PPE	Personal Protective Equipment
qPCR	Quantitative polymerase chain reaction
RNA	Ribonucleic acid
RT	Reverse transcription
VOC	Varients of concern

analytical sensitivity: quotient of the change in an indication and the corresponding change in the value of a quantity being measured (ISO 15193)

analytical specificity: ability of a measurement procedure to determine solely the quantity it purports to measure (ISO 15193)

Clinical (Diagnostic) Sensitivity: ability of an IVD examination procedure to identify the presence of a target marker(s) in individuals with a particular disease or condition

Clinical (Diagnostic) Specificity ability of an IVD examination procedure to recognise the absence of a target marker(s) in individuals with a particular disease or condition

Positive Percent Agreement: the proportion of non-reference standard positive subjects in whom the new test is positive.

Negative Percent Agreement: the proportion of non-reference standard negative subjects in whom the new test is negative

Positive Predictive Value: the proportion of patients with positive test results who have the target condition (as determined by the reference standard)

Negative Predictive Value: the proportion of patients with negative test results who do not have the target condition (as determined by the reference standard)