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	15-10-2020	Initial document

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The purpose of a Target Product Profile "TPP"

Target product profiles (TPP) outline the 'profile' or characteristics of a target product that is aimed at a particular disease or diseases. TPPs state intended use, target populations and other attributes of products, including safety and performance-related characteristics. They help guide industry development towards desired characteristics. A TPP provides a common foundation for the development of tests and contains sufficient detail to allow device developers and key stakeholders to understand the characteristics a test must have to be successful for the particular intended use. Included is a description of (1) the preferred and (2) the minimally acceptable profiles based on the intended use, setting of use, and intended user, with respect to the performance and operational characteristics expected of the target products. As new scientific evidence is generated, this TPP may require further review and revision.

TPPs for detection of SARS-CoV-2 in order to diagnose COVID-19

These product profiles have been developed to assist manufacturers to design and deliver tests that might be useful in support of the UK COVID-19 testing strategy. How closely a product matches the profile may inform procurement and regulatory decision making. Any deviation 'from target specification must be fully justified. Production lead time may also factor into decision making.
This TPP is for laboratory based SARS-CoV-2 Viral detection tests.

It should be noted that, a different TPP could apply for different scenarios as such the contents of the TPP in this document are restricted. This TPP contains profiles based on our best information, but the science and use requirements are rapidly evolving. Manufacturers should ensure they are working to the most recent TPP and the most recent science.

Clinical performance requirements

This is a specification of the clinically acceptable performance requirements for SARS-CoV-2 viral detection tests. It sets out the clinical requirements based on the consensus of what is 'minimally acceptable' in the opinion of UK healthcare professionals. A test kit with specifications other than this may not be suited to support the UK testing strategy.

The intended use of the assays that match this profile (or one that does not yet meet the specifications but looks promising) is to aid in the management of individuals with a current SARS-CoV-2 infection by detection of SARS-CoV-2 nucleic acid in human samples. Assays that don't yet meet the specifications but look promising may require further technical and clinical validation.

The acceptable criteria for clinical sensitivity and specificity are an initial estimate of minimally acceptable performance based on current expert opinion in a potentially limited number of use cases. Examples of potential use cases of such devices from the Foundation for Innovative New Diagnostics (FIND) can be found here.

To ensure ongoing public safety and value for money, procurement and deployment of tests should consider the specific clinical decision the test is being used to make, the prevalence of SARS-CoV-2 within the intended test population, as well as the potential consequences of false positives and false negatives. The acceptable clinical sensitivity and specificity may need to be higher for some uses of the tests. For example, in populations with a low prevalence of COVID-19, very high specificity may be needed to

increase assurance that a positive test result is a true positive. The impact of changing sensitivity, specificity and prevalence on the numbers of false positives and negatives can be seen in tables below (Annex 2).

These specification criteria are based on similar TPPs published by the World Health Organisation (WHO), Program for Appropriate Technology in Health (PATH), and FIND for in-vitro diagnostics (IVDs) for other diseases.

Future developments
These profiles are subject to review and change, as we gain a greater knowledge of SARS-CoV-2, the disease it causes (COVID-19) and our needs for an effective response. They may need to be updated at short notice.

As our knowledge and understanding of the disease improves and the UK clinical needs change, so may the TPP. A test that meets this version of the TPP may not meet future versions. Manufacturers should ensure that they are working to the most recent TPP.

It is expected that as more well characterised samples become available, then test performance can be established on a higher number and more diverse samples.

Key to Table

Acceptable: Defines the minimum acceptable feature.

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.

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

Key feature	Desired	Acceptable	Comment
SCOPE			
Intended use	Multiplex - Determining current infection by detecting SARS-CoV-2 virus in samples from people of all ages at any point during active infection and differentiating from other respiratory infections	Determining current SARS-CoV-2 infection by detection of SARS-CoV-2 virus in samples from people of all ages during the active phase of infection.	Active infection may be asymptomatic or symptomatic
Target population	People with or without clinical signs associated with SARS-CoV-2 infection	People with clinical signs associated with SARS-CoV-2 infection	
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 technician or scientist.		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

			test types that are appropriate for that setting.
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 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..		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 marking. Specifications for general reagents that can be used with open or closed systems must be clearly defined
SARS-CoV-2 Target	Dual (or more) SARS-CoV-2 RNA	Single SARS-CoV-2 RNA	
Analyte	Multiplex panel for a range of infectious respiratory viruses Detection and differentiation of SARS-CoV-2, influenza A virus, and/or influenza B virus, RSV A & B	SARS CoV 2 only	Multiplex systems must be able to clearly distinguish between targets included in the panel.
Sample type	Oral Fluid	Nasopharyngeal or oropharyngeal swabs, lower respiratory tract aspirates, bronchoalveolar lavage, nasopharyngeal wash/aspirate or nasal aspirate	Methods not using invasive swabs are desirable due to the individuals discomfort, pre-analytical errors

			Consideration should be given to compatibility of sample with collection media/buffers and assay performance Sample types must be validated as part of the performance assessment
Compatible sample collection	Test is validated for use with saliva and/or non-propriety collection media	Test is validated for use with a variety of non-propriety sample collection media e.g. viral transport medium, inactivation medium, dry swabs, and saline in addtion to propriety media	Supply chain constraints
Result output	Semi quantitative	Qualitative	Reference RNA/DNA materials are now available from NIBSC[1] for RT-qPCR. Some reference materials may perform poorly in RT-LAMP assays because of intact fragment length availability. This may be revised when an International Standard becomes available.
Size	Free standing or benchtop systems		Larger systems may have higher capacity for sample processing.
Power requirement	Standard mains power supply with UPS and the capability for battery power.	Standard mains power supply	
Internal controls	Whole process positive controls, negative controls, internal and external controls are required to confirm	Should include positive controls and negative controls with option to include internal	Invalid results may be due to sampling technique or presence of biological inhibitors.

	validity end-end processing and clearly identify inhibitory or cellular deficient results as invalid.	controls/external controls in a single or multiplex format.	.
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 IVD regulations. 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	
PERFORMANCE CHARACTERISTICS			
Clinical (diagnostic) sensitivity (or Positive Percent Agreement)	For RNA extraction based assays a greater than 99% (with 95% two-sided confidence interval entirely above 97%).	For RNA extraction based assays a greater than 95% (with 95% two-sided confidence interval entirely above 90%).	At least 150 positive clinical samples with viral loads that span the upper and lower limit of detection for the comparator assay The samples should cover a clinically meaningful range of viral loads and the

			percentages of each concentration (low, medium and high) used should match the concentrations anticipated in the test population.
Clinical (diagnostic) specificity (or Negative Percent Agreement)	For RNA extraction based assays and those assays which detect SARS-CoV-2 directly from clinical samples a greater than 99% (with 95% two-sided confidence interval entirely above 97%). *	For RNA extraction based assays and those assays which detect SARS-CoV-2 directly from clinical samples a greater than 95% (with 95% two-sided confidence interval entirely above 90%).	At least 250 negative clinical samples.
Comparison method	RT-qPCR or dPCR reference methods.	Reference method against which the Negative/Positive Percent Agreement is calculated	The comparison should consider the effect of treatment or storage on virus material prior to use and the impact this may have had on the ability of that assay to detect inactivated virus/degraded RNA. Sample must be processed in accordance with the instructions for use
Analytical specificity	No clinically relevant cross reactivity or interference	No clinically relevant cross reactivity or interference Minimal interference caused by common interferents at clinically relevant concentrations (dependant on sample type and analyte)	See annex 1 for list Demonstrated specificity in the presence of other respiratory pathogens, Flu A/B, RSV, hMPV etc.

Analytical sensitivity (Limit of Detection (LOD)	≤100 SARS-CoV-2 copies/mL	≤ 1000 SARS-CoV-2 copies/mL	Positive samples for which the quantity value and measurement uncertainty have been assigned (i.e. by dPCR) should be used to characterize the true positive detection rate. Where a different unit of measurement is used (e.g. copies/swab, ng/ml) equivalence must be demonstrated and copies/ml equivalent stated in the validation data. International Standards should be used when available to report LOD Treatment of virus material on ability of the technology to detect sample needs to be considered particularly in the case of RT-LAMP assays.
Clinical utility	Evidence that using the test improves system and individual outcomes (for example, time to diagnosis, subject's experience, use of pre-cautionary COVID-19 isolation facilities).		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
Turnaround time	Less than 90 minutes from sample to result	Less than five hours from sample to result	The time is from receipt of sample in test laboratory.
Throughput	More than 200 tests in unit per 4 hours	More than 50 tests per unit in 4 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 standard laboratory equipment (centrifuge, vortex, pipette etc).		
Biosafety	Buffers provided with kit are proven to inactivate SARS-CoV-2 and any other respiratory viruses in scope of assay enabling entire process to be carried out outside of CL3 or 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 ^{o}C)	Storage of kit and reagents at -20^{o}C and above for at least 12 months. Stable for 12 hours once removed from cold storage.	Packaging to be as compact as possible to facilitate 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 ^{o}C		

Connectivity	Wireless connectivity into NHS LIMS systems	Cable connectivity into NHS LIMS system	Results may need to be transferred by digital media e.g. CSV files
Presentation of results	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.
Volume of sample	Depends on sample type, but no more than 0.5mL		
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 than half day training needed for laboratory staff	Less than one day of training needed	
OTHER			
Immediate supply volumes (Tests per week, within 4 weeks)	10,000 tests per day	5000 tests per day	
Label and Instructions for Use	Conforms to IVD Directive and relevant harmonised standards		
Regulatory status	CE marked	Exempt according to Article 9 para 12 or para 13 of IVD Directive	

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		

1. National Institute of Biological Standards and Control (NIBSC) is developing a number of reference materials including a candidate International Standard for SARS CoV 2 nucleic acid.. Refer to website https://www.nibsc.org/science_and_research/virology/centre_for_aids_reagents/covid-19_reagents.aspx

ANNEX 1: ASSAY VALIDATION

Establishing Performance Characteristics.

It is recommended that the following aspects are considered when designing and validating the assay.

- Reference material should be used to establish performance, including standard validation panels, quality control materials and proficiency testing materials
- Some technologies may require dilution series of untreated whole virus then comparing with dPCR. Treated material may artificially lower sensitivity of a LAMP assay
- When establishing analytical specificity, the following should be considered:
    - Prepandemic samples,
    - Other coronavirus, SARS-CoV-1,
    - hCoV 229E, OC43, HKU1, NL63 epitopes /genome
    - Adenovirus (e.g. C1 Ad. 71)
    - Human Metapneumovirus (hMPV)
    - Parainfluenza virus 1-4
    - Influenza A & B
    - Enterovirus (e.g. EV68)
    - Respiratory syncytial virus
    - Rhinovirus
    - Middle East Respiratory Syndrome (MERS)
    - *Chlamydia pneumoniae*
    - *Haemophilus influenzae*
    - *Legionella pneumophila*
    - *Mycobacterium tuberculosis*
    - *Streptococcus pneumoniae*
    - *Streptococcus pyogenes*
    - *Bordetella pertussis*
    - *Mycoplasma pneumoniae*
    - *Pneumocystis jirovecii (PJP)*
    - *Epstein Barr Virus*

- 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 clinical range of haematocrit values

Post-market performance considerations for probes and primers

Manufacturers should consider monitoring for potential genetic change to ensure probes and primers are not adversely affected by such events. In silico analysis may aid ongoing monitoring.

Annex 2: Diagnostic accuracy considerations

When considering procurement and deployment of devices for any clinical and public health use-case, it is recommended to consider the maximum number of false positives and false negatives that would be acceptable for the new test based on the possible consequences of these misdiagnoses.

The table below presents the numbers of false positives and negatives in a cohort of fixed size (10,000) with varying prevalence of COVID-19 (NPV/PPV rounded to nearest whole number).
Therefore, for a test with a sensitivity of 80% and specificity of 95%**:**

COVID-19 prevalence	**False Positives**	**Positive predictive value** (proportion of people with positive results who have COVID-19)	**False Negatives**	**Negative predictive value** (proportion of people with negative results that don't have COVID-19)
1%	495	14%	20	100%
5%	475	46%	100	99%
10%	450	64%	200	98%
50%	250	94%	1000	83%

It should also be noted that sensitivity and specificity values estimated in a particular population (i.e. intensive care patients) may not be generalisable to other populations (i.e. general practice) with a different prevalence of COVID-19, if these populations are made up of people with less or more severe COVID-19. For example, accuracy estimates generated in a population of people with early symptoms of COVID-19 may be higher, due to viral load, than a test would achieve in a population of people with no symptoms of the condition.

Prevalence 1%

Numbers per 10,000 tested

			Sensitivity					
		Test result	**98%**	**95%**	**90%**	**85%**	**80%**	**75%**
Specificity	98%	False Positives	198	198	198	198	198	198
		False Negatives	2	5	10	15	20	25
	95%	False Positives	495	495	495	495	495	495
		False Negatives	2	5	10	15	20	25
	90%	False Positives	990	990	990	990	990	990
		False Negatives	2	5	10	15	20	25
	85%	False Positives	1,485	1,485	1,485	1,485	1,485	1,485
		False Negatives	2	5	10	15	20	25
	80%	False Positives	1,980	1,980	1,980	1,980	1,980	1,980
		False Negatives	2	5	10	15	20	25
	75%	False Positives	2,475	2,475	2,475	2,475	2,475	2,475
		False Negatives	2	5	10	15	20	25

Prevalence 5%

Numbers per 10,000 tested

			Sensitivity					
		Test result	**98%**	**95%**	**90%**	**85%**	**80%**	**75%**
Specificity	98%	False Positives	190	190	190	190	190	190
		False Negatives	10	25	50	75	100	125
	95%	False Positives	475	475	475	475	475	475
		False Negatives	10	25	50	75	100	125
	90%	False Positives	950	950	950	950	950	950
		False Negatives	10	25	50	75	100	125
	85%	False Positives	1,425	1,425	1,425	1,425	1,425	1,425
		False Negatives	10	25	50	75	100	125
	80%	False Positives	1,900	1,900	1,900	1,900	1,900	1,900
		False Negatives	10	25	50	75	100	125
	75%	False Positives	2,375	2,375	2,375	2,375	2,375	2,375
		False Negatives	10	25	50	75	100	125

Prevalence 10%

Numbers per 10,000 tested

			Sensitivity					
		Test result	**98%**	**95%**	**90%**	**85%**	**80%**	**75%**
Specificity	98%	False Positives	180	180	180	180	180	180
		False Negatives	20	50	100	150	200	250
	95%	False Positives	450	450	450	450	450	450
		False Negatives	20	50	100	150	200	250
	90%	False Positives	900	900	900	900	900	900
		False Negatives	20	50	100	150	200	250
	85%	False Positives	1,350	1,350	1,350	1,350	1,350	1,350
		False Negatives	20	50	100	150	200	250
	80%	False Positives	1,800	1,800	1,800	1,800	1,800	1,800
		False Negatives	20	50	100	150	200	250
	75%	False Positives	2,250	2,250	2,250	2,250	2,250	2,250
		False Negatives	20	50	100	150	200	250

Prevalence 50%

Numbers per 10,000 tested

			Sensitivity					
		Test result	**98%**	**95%**	**90%**	**85%**	**80%**	**75%**
Specificity	98%	False Positives	100	100	100	100	100	100
		False Negatives	100	250	500	750	1,000	1,250
	95%	False Positives	250	250	250	250	250	250
		False Negatives	100	250	500	750	1,000	1,250
	90%	False Positives	500	500	500	500	500	500
		False Negatives	100	250	500	750	1,000	1,250
	85%	False Positives	750	750	750	750	750	750
		False Negatives	100	250	500	750	1,000	1,250
	80%	False Positives	1,000	1,000	1,000	1,000	1,000	1,000
		False Negatives	100	250	500	750	1,000	1,250
	75%	False Positives	1,250	1,250	1,250	1,250	1,250	1,250
		False Negatives	100	250	500	750	1,000	1,250

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

analytical sensitivity: sensitivity of a measurement procedure quotient of the change in a measurement indication and the corresponding change in a value of a quantity being measured
analytical specificity: selectivity of a measurement procedure capability of a measuring system, using a specified measurement procedure, to provide measurement results for one or more measurands which do not depend on each other nor on any other quantity in the system undergoing measurement
Clinical (Diagnostic) Sensitivity: ability of an IVD examination procedure to identify the presence of a target marker associated with a particular disease or condition
Clinical (Diagnostic) Specificity ability of an IVD examination procedure to recognise the absence of a target marker associated with a particular disease or condition
(the above definitions of performance characteristics taken from BS EN ISO 18113-1:2011, In vitro diagnostic medical devices — Information supplied by the manufacturer (labelling): Terms, definitions and general requirements)

Positive Percent Agreement: calculated in the same way as Clinical (Diagnostic) Sensitivity, but indicate that a non-reference standard was used

Negative Percent Agreement: calculated in the same way as Clinical (Diagnostic) Specificity, but indicate that a non-reference standard was used