Medicines & Healthcare products Regulatory Agency

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TARGET PRODUCT PROFILE

Point of Care SARS-CoV-2 Detection Tests

Version Control

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The purpose of a Target Product Profile "TPP"

Target product profiles (TPP) outline the desired 'profile' or characteristics of a target product that is aimed at a particular disease or diseases. TPPs state intended use, target populations and other desired 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 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 COIVD-19 testing strategy. How closely a product matches the profile may inform procurement and regulatory decision making. Any deviation from existing standards must be fully justified. Production lead time may also factor into decision making.
Implementation of the testing strategy will be enhanced by parallel testing capability offered through the availability of point of care tests (POCT) that can quickly detect the SARs-CoV-2 virus in a near patient setting, allowing health and care professionals to efficiently triage patients depending on their likelihood of being infected.

Such tests require taking a small sample of bodily fluid and looking for the presence of viral nucleic acids or antigens specific to SARS-CoV-2, the causative agent of COVID-19. When available these tests could be used across the broad spectrum of health and care settings and eventually in non-healthcare contexts, such as schools, airports and prisons. They should thus be safe, simple, robust and have a rapid time to test result.

Point of Care SARS-CoV-2 tests for other purposes are not part of this profile and might include:

- to provide a confirmatory diagnosis of patient's current SARS-CoV-2 infection status
- to prognose a patient's likely outcome, including disease severity or survival.
- to predict or monitor a patient's likely response to treatment.
- to differentially diagnose SARs-CoV-2 from other common febrile or influenza-like disease pathogens, through the use of a multiplex assays.
- rapid laboratory tests to augment clinical laboratory capacity and turn around time.
- self-tests to be perfomed by a lay individual.

It should be noted that for each of these intended use scenarios, a different TPP could apply. As such the contents of the TPPs in this document are restricted. These TPPs are 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 requriements for point of care 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 IVD industry, healthcare professionals and medical device regulators given the emergency situation. A test kit with other specifications than this may not be suitable to support the UK testing strategy.

The intended use of assays that match these profiles (or one that does not yet meet the specifications but looks promising) is to aid in the triage of patients with a current SARS-CoV-2 infection by detection of SARS-CoV-2 nucleic acids or antigens in human samples.

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 FIND can be found here.

To ensure ongoing public safety and value for money, procurement and deployment of tests should take into account consideration of the specific clinical decision and pathway changes the test is being used to make, the current and future prevalence of SARS-CoV-2 within the intended test population, as well as the potential consequences of false positives and false negatives. For example, 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 even higher specificity may be needed to prevent the probability that a positive test result is a true positive (positive predictive value) from being unacceptably low.

Annex 2 provides tables 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. For example, tests with a low sensitivity may have limited utility in ruling-out SARS-CoV-2 in patients, especially if rule-out may expose others to infection. Similarly, tests with a low specificity may have limited utility in ruling-in SARS-CoV-2 in patients, especially if this may expose uninfected patients to infection, for example by being transferred to a COVID ward.

When used for triage, it may be possible to reduce the potentially harmful consequences of an insensitive or unspecific test, by confirming negative or positive POC results using a more accurate, but slower diagnostic test, such as conventional lab based methods. The advantage of the POC test here could be that at least a

proportion of people with, or without, COVID-19 can be managed faster than relying on conventional lab based testing alone.

These specification criteria are based on similar Target Product Profiles published by the World Health Organisation, PATH, and FIND for IVDs to other diseases. Each of these organisations has extensive experience with establishing TPPs for simple, rapid diagnostic tests.

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. When assessing options of available test refer to the latest version of TPP published.

As the market matures, it is expected that test formats will adapt – for example, SARS-CoV-2 may be included in respiratory panels or the target user may include people other than healthcare professionals or tests requiring less maintenance may become available.

It is also expected that as more well curated and well characterised samples become available, then test performance can be established on higher numbers of samples.

Other solutions

Ideally, products should be designed to achieve as many of the optimal characteristics as are feasible, while still satisfying the minimal criteria for all defined features. However, a test that does not yet meet all these profiles may still have a role in supporting the UK testing strategy.

Access to a UK-wide, sufficiently constituted panel of samples (saliva, urine, blood) would be helpful in delivering evaluations.
This could mean either

1. sufficient samples to assess analytical performance – including highly characterised SARS-CoV-2 calibration and control materials and samples containing likely interferent or cross-reactants.
2. a standard set of samples to validate the clinical performance of a test, selected to represent a UK population that the test will be used in.

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
Point of Care SARS-CoV-2 Detection testing

Key feature	Desired	Acceptable	Comment
SCOPE			
Intended use	Aid in triage of current SARS-CoV-2 infection by detection of SARS-CoV-2 nucleic acids or antigens in samples from people of all ages at any point during active infection	Aid in triage of current SARS-CoV-2 infection by detection of SARS-CoV-2 nucleic acids or antigens in samples from people of all ages during the acute phase of infection.	
Target population	People with or without clinical signs and symptoms associated with SARS-CoV-2 infection, if testing is appropriate. .	People with clinical signs and symptoms associated with SARS-CoV-2 infection	
Target user	Trained healthcare professional (i.e. one of the 10 health and social care professional bodies that are overseen by the professional standards authority)		A healthcare professional will select the right test to use with the patient, perform the test and then interpret and communicate the results. There may be some scope for supervised self-sampling where the sample collection device is CE marked for this purpose (eg saliva samples) Full training appropriate to the intended user is required.

Target use Setting	At the point of care in secondary, primary and community healthcare settings Non-healthcare settings (e.g. schools, airports, prisons)		
TEST DESIGN CHARACTERISTICS			
Test format	A standardised kit that contains all materials required for the procedure in a self-contained kit that includes controls, reagents and Instruction for Use All accessories needed to perform the assay and sample collection included	A standardised kit that contains all materials required for the procedure in a self-contained kit that includes controls, reagents and Instruction for Use. Accessories needed to perform the assay provided separately (eg sample collection).	All accessories need to be validated for use in combination with the test as part of the CE marking.
Target analyte	Dual (or more) SARS-CoV-2 RNA or antigen targets	Single SARS-CoV-2 RNA or antigen target	
Sample type	Sputum, saliva or other method not using invasive swab	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 patient discomfort, pre-analytical errors and issues with supply chain.
Result output	Semi quantitative	Qualitative	Reference RNA materials are now available from NIBSC. This may be revised when an International Standard becomes available.
Size	Handheld	Desktop, portable.	
Power requirement	No power source needed, or a rechargeable and replaceable battery	Standard mains power supply	
Internal controls	Required to confirm validity of test and any processing and clearly identify invalid results as invalid		Invalid results may be due to sampling technique

Technical failure rate	Less than 1%	Less than 5%	Demonstrated through post market surveillance Higher failure rates can lead to delays and lack of confidence with end users. Low test failure rates are more important in settings where users have difficullty repeating tests.
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 patient/donor identification must be feasible.	
PERFORMANCE CHARACTERISTICS			
Clinical (diagnostic) sensitivity (or Positive Percent Agreement)	Greater than 97% (within confidence intervals of 93-100%)	Greater than 80% (within 95% confidence intervals of 70-100%	At least 150 positive clinical samples The samples should cover a clinically meaningful range of viral loads (i.e. should be from people with high, medium and low viral load) that represents the population the test is intended to be used in. For tests with lower sensitivity, it is envisaged that when used in practice people with negative results will need confirmatory checking by an additional test
Clinical (diagnostic) specificity (or Negative Percent Agreement)	Greater than 99% (within confidence intervals of 97-100%)	Greater than 95% (within 95% confidence intervals of 90-100%)	At least 250 negative clinical samples. For tests with lower specificity, it is envisaged that when used in practice

			people with positive results will need confirmatory checking by an additional test
Comparison method	A composite clinical reference standard or dPCR reference method.	A validated CE marked laboratory method in current clinical use, against which the Negative/Positive Percent Agreement is calculated	For samples in which the POC test is positive and comparison method is negative, further testing should be done to try and explain the discordant result (for example, repeating the sample run on both tests or using a third method, if available).
Analytical specificity	No clinically relevant cross reactivity or interference	No clinically relevant cross reactivity to other Coronavirus species. Minimal interference caused by common interferents at clinically relevant concentrations (dependant on sample type and analyte)	See annex 1 for list
Analytical sensitivity (Limit of Detection)	Fewer than 100 SARS-CoV-2 copies/mL	Fewer than 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 (eg copies/swab, ng/ml) equivalence must be demonstrated
Clinical utlity	Evidence that using the test improves system and patient outcomes (for example, time to diagnosis, patient 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

Turn around time	Less than 30 minutes from sample to result	Less than 2 hours from sample to result	
Throughput	More than 100 tests per unit per 12 hours	More than 6 tests per unit per 12 hours	
TEST PROCEDURE CHARACTERISTICS			
Hands on time	Less than 2 minutes	Less than 20 minutes	
Sample collection equipment	Included with the test	Uses standard NHS consumables	All accessories need to be validated for use in combination with the test as part of the CE marking.
Sample processing and handling	No sample processing steps required	Up to 2 standardised sample-processing steps, but these must not take longer than 15 minutes or require additional laboratory equipment (centrifuge, vortex, pipette etc).	
Biosafety	Standard PPE and safety procedures need to be followed. No need for BSL 2 or 3 laboratory facilities. Evidence that live virus is deactivated early in the process.		
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 2-8 ^{o}C for at least 12 months. Stable for 12 hours once removed from cold storage.	
Assay end point stability (time window during which signal remains valid)	up to 1 hour	up to 30 minutes	In busy testing environments, the need for a stable end point is imperative.
Operating conditions	15 to 30 ^{o}C		
Connectivity	Wireless connectivity into NHS LIMS systems	Not required	

Presentation of results		Human readable, easy to capture and able to record public health data	
Reader to reader variation	Doesn't require reading	Readers should be able to correctly interpret true positive results near the limit of detection	
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		
Training needs (Time dedicated to training session for end users)	No additional training needed	Less than half day of training needed	
OTHER			
Immediate supply volumes (Tests per week, within 4 weeks)	5000 tests per day	1000 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 year or >5000 samples; an alert should be included to indicate when maintenance is needed.	Preventive maintenance should not be needed until after 1 year or 1000 samples; an alert should be included to indicate when maintenance is needed.	

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.

- Reference material should be used to establish performance, including standard validation panels, quality control materials and proficiency testing materials
- When establishing analytical specificity, the following should be considered:
    - Prepandemic samples,
    - other coronavirus, SARS-CoV-1,
    - hCoV 229E, OC43, HKU1, NL63 epitopes
    - 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.

  Endogenous substances
    - Hemoglobin
    - Bilirubin
    - Protein
    - Triglycerides
    - Hematocrit
    - Rheumatoid Factor
    - Antibodies developed against protein expression system used to generate recombinant antigens

  Exogenous substances

  •Medications most often prescribed in the patient population for which the test is ordered

  •Recommended anticoagulants e.g. EDTA

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 that would be acceptable for the new test based on the possible consequences of these misdiagnoses.

The table below presents the numbers of false positves 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.

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Prevalence **1%**

SENSITIVITY

Numbers per 10,000 tested

SPECIFICITY	Test result	98%	95%	90%	85%	80%	75%
98%	False +ves	198	198	198	198	198	198
	False -ves	2	5	10	15	20	25
95%	False +ves	495	495	495	495	495	495
	False -ves	2	5	10	15	20	25
90%	False +ves	990	990	990	990	990	990
	False -ves	2	5	10	15	20	25
85%	False +ves	1,485	1,485	1,485	1,485	1,485	1,485
	False -ves	2	5	10	15	20	25
80%	False +ves	1,980	1,980	1,980	1,980	1,980	1,980
	False -ves	2	5	10	15	20	25
75%	False +ves	2,475	2,475	2,475	2,475	2,475	2,475
	False -ves	2	5	10	15	20	25

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Prevalence **5%**

SENSITIVITY

Numbers per 10,000 tested

SPECIFICITY	Test result	98%	95%	90%	85%	80%	75%
98%	False +ves	190	190	190	190	190	190
	False -ves	10	25	50	75	100	125
95%	False +ves	475	475	475	475	475	475
	False -ves	10	25	50	75	100	125
90%	False +ves	950	950	950	950	950	950
	False -ves	10	25	50	75	100	125
85%	False +ves	1,425	1,425	1,425	1,425	1,425	1,425
	False -ves	10	25	50	75	100	125
80%	False +ves	1,900	1,900	1,900	1,900	1,900	1,900
	False -ves	10	25	50	75	100	125
75%	False +ves	2,375	2,375	2,375	2,375	2,375	2,375
	False -ves	10	25	50	75	100	125

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Prevalence **10%**

SENSITIVITY

Numbers per 10,000 tested

SPECIFICITY	Test result	98%	95%	90%	85%	80%	75%
98%	False +ves	180	180	180	180	180	180
	False -ves	20	50	100	150	200	250
95%	False +ves	450	450	450	450	450	450
	False -ves	20	50	100	150	200	250
90%	False +ves	900	900	900	900	900	900
	False -ves	20	50	100	150	200	250
85%	False +ves	1,350	1,350	1,350	1,350	1,350	1,350
	False -ves	20	50	100	150	200	250
80%	False +ves	1,800	1,800	1,800	1,800	1,800	1,800
	False -ves	20	50	100	150	200	250
75%	False +ves	2,250	2,250	2,250	2,250	2,250	2,250
	False -ves	20	50	100	150	200	250

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Prevalence **50%**

SENSITIVITY

Numbers per 10,000 tested

SPECIFICITY	Test result	98%	95%	90%	85%	80%	75%
98%	False +ves	100	100	100	100	100	100
	False -ves	100	250	500	750	1,000	1,250
95%	False +ves	250	250	250	250	250	250
	False -ves	100	250	500	750	1,000	1,250
90%	False +ves	500	500	500	500	500	500
	False -ves	100	250	500	750	1,000	1,250
85%	False +ves	750	750	750	750	750	750
	False -ves	100	250	500	750	1,000	1,250
80%	False +ves	1,000	1,000	1,000	1,000	1,000	1,000
	False -ves	100	250	500	750	1,000	1,250
75%	False +ves	1,250	1,250	1,250	1,250	1,250	1,250
	False -ves	100	250	500	750	1,000	1,250

ANNEX 3 Glossary

POC/POCT point of care/point of care tests
RNA Ribonucleic acid
dPCR Digital polymerase chain reaction
LoD Limit of Detection
PPE Personal Protective Equipment
BSL Biological Safety Level
LIMS Laboratory Information Management System

Point of care test (also known as near patient test): an in vitro diagnostic medical device that is not intended for self-testing but is intended to perform testing outside a laboratory environment, generally near to, or at the side of, the patient by a health professional
Self-test:an in vitro diagnostic medical device intended to be used by a layperson

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 characterisitics 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