TARGET PRODUCT PROFILE

In Vitro Diagnostic (IVD) self-tests for the detection of SARS-CoV-2 in people without symptoms

Version Control

Version	Date Issued	Description
1.0	19/05/2021	Initial document
2.0		

The purpose of MHRA Target Product Profiles

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 TPPs 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 in vitro diagnostic self-tests for use as part of UK government national testing programmes or accredited private testing services for the following purposes:

1. Self-testing to help **rule in** SARS-CoV-2 infection in people without symptoms at home or in other community settings (i.e. non-healthcare environments).

And/or

2. Self-testing to help **rule out** SARS-CoV-2 infection in people without symptoms at home or in other community settings.

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

1. The target population and users (e.g. children, young people, adults, older people)
2. The setting (e.g. home, workplace, school, airport, social care)
3. The intervention decision being informed (e.g. release from isolation, contact tracing, infection control measures etc).

This TPP does not consider tests for other purposes, such as in the following possible scenarios:

- Self-tests for “over the counter” general sales direct to consumers.
- Point of care tests to be performed by a professional (full definitions) in a health and/or social care setting.
- Rapid laboratory tests to augment clinical laboratory capacity and turnaround time.
- Tests conducted in a laboratory using self-sampled (self-collected) specimens.
- Provide a confirmatory diagnosis of patient’s current SARS-CoV-2 infection status.
- Prognose a patient’s likely outcome, including disease severity or survival.
- Predict or monitor a patient’s likely response to treatment.
- Differentially diagnose SARS-CoV-2 from other common febrile or influenza-like disease pathogens, through the use of a multiplex assays.

Clinical performance requirements

This specification outlines the performance requirements for Self-test IVDs for the detection of SARS-CoV-2. The intended use of assays that match these profiles is to identify SARS-CoV-2 infection or the absence of infection, through the detection of SARS-CoV-2 specific markers such as antigens, nucleic acids or other analytes.

The TPP sets out the requirements based on the consensus of what is “desired” and minimally “acceptable” in the opinion of healthcare professionals 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.

For example, in community populations with a low prevalence of infection high specificity will be needed for tests to help **rule in** Sars-CoV2, to limit virus free people from being misclassified as having current infection. Similarly, very high test sensitivity is essential for tests to help **rule out**, to limit infected individuals being misclassified as virus free and further transmitting the disease.

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 (e.g. new variants), 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

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 should be considered

TARGET PRODUCT PROFILE
COVID-19
SELF-TEST[1] for SARS-CoV-2

Key Feature	Desired	Acceptable	Comment
SCOPE			
Intended Function(s)	Self-test used to: - help identify current SARS-CoV-2 infection (**rule in)** AND/OR - help determine the absence of current SARS-CoV-2 infection (**rule out**).		**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. A negative result from a “rule in” test should not be used to change infection control behaviours, such as social distancing and self-isolation. Information is needed to prevent foreseeable misuse and

[1] Self-Test: A test intended by the manufacturer to be able to be used by lay persons in a home environment.

			ensure users are aware that a negative test will not exclude the risk of having, developing or transmitting SARS-CoV-2. Similarly, a positive result from a “rule out” test will likely require confirmation by another method depending on the specificity of the test and the pre-test probability of the population.
Target Population	Adults and all school age children (≥3 years) without symptoms. Adults and children without appropriate physical and mental capacity should have their test conducted or supervised by an appropriate individual.	Adults and secondary school age children (≥11 years) without symptoms. Adults and children without appropriate physical and mental capacity should have their test conducted or supervised by an appropriate individual.	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 aged 3-11 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 (i.e. self-tested, supervised, or performed by an adult on a child). 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.

			Manufacturers should put measures in place to prevent home self-tests intended for use in people without symptoms being misused by people with COVID-19 symptoms.
Target user	An individual who is capable of using the device without training, but with reference to the included labelling and instruction for use.		Tests intended for use, or supervised use, by appropriately trained professionals should refer to TPPs for point of care testing. Manufacturers should consider the needs and abilities of the target user group, especially any characteristics protected under the Equality Act 2010.
Target use setting	Non-healthcare settings (e.g. at home, social care, schools, prisons, workplaces, universities, airports and other transport hubs etc).		
TEST DESIGN CHARACTERISTICS			
Test format	A standardised kit that contains all materials and equipment required for the procedure in a self-contained kit that includes controls, non-hazardous reagents and Instruction for use.	A standardised kit that contains all materials required for the procedure in a self-contained kit that includes controls, non-hazardous reagents and Instruction for use. Other equipment required, for example a mobile phone with camera, timer/clock, tissue, hand sanitiser.	All accessories need to be validated for use in combination with the test.
Target Analyte (Measurand)	Dual (or more) SARS-CoV-2 targets (e.g. nucleic acid(s), antigen(s) or other targets)	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 multiple 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. 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 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.
Result output	Qualitative		The result output should consider the intended user and how they will interpret, report, use and notify the results in accordance with public health law around notification. Quantitative or Semi-Quantitative tests will need to justify why such a result is appropriate and provide robust evidence supporting useability, as above.
Internal control	Required to confirm the validity of tests and any processing.	Required to confirm the validity of tests and any processing.	Invalid results may be due to sampling technique or the presence of interferents or other factors such as incorrect storage or use of the device

	Includes sample adequacy (i.e. human target), process and reaction controls. Clearly identifies invalid results as invalid.	Clearly identifies invalid results as invalid.	
Pack size	A range of kit sizes from 1-25 tests/kit	No more than 25 tests/kit	
Need for calibration/ spare parts	None should be needed prior to performing the test		Manufacturers might consider the inclusion of an extra collection device
PERFORMANCE CHARACTERISTICS			
Clinical (diagnostic) Sensitivity	*For tests to help rule in:* **≥95%** (with 95% two-sided confidence interval entirely above 90%). At a prevalence of 1%, for every 100,000 tests done, 50 cases of SARS-CoV-2 infection could be missed and 950 cases detected.	*For tests to help rule in:* **≥80%** (with 95% two-sided confidence interval entirely above 70%). At a prevalence of 1%, for every 100,000 tests done, 200 cases of SARS-CoV-2 infection could be missed and 800 cases detected.	At least **150** SARS-CoV-2 positive cases (per sample type). The population and user group should be representative of the claimed target population and user groups, see “Clinical Performance Evaluation” section below. Repeated testing strategies might achieve greater overall clinical sensitivity than single cross-sectional measurement strategies, meaning that an otherwise low sensitivity test might achieve the acceptable or desirable clinical sensitivity requirement when used in such a strategy. Appropriate clinical study designs, not modelling alone, would be required to demonstrate such repeated testing performance claims. In particular, assessment should focus on test-patterns (e.g. a good daily test pattern for “current” infection would

	For tests to help rule out: **≥99.9%** (with 95% two-sided confidence intervals entirely above 99%). At a prevalence of 1%, for every 100,000 tests done, 1 case of SARS-CoV-2 infection could be missed and 999 cases detected.	*For tests to help rule out:* **≥97%** (with 95% two-sided confidence intervals entirely above 95%). At a prevalence of 1%, for every 100,000 tests done, 30 cases of SARS-CoV-2 infection could be missed and 970 cases detected.	be NNPPPPNNN and pattern with false positives might be PNNNNPNNN). Context of use for asymptomatic screening should specify and be evaluated using defined inter-screen-intervals (e.g. every 24 hours, 2 to 3 times per week or weekly). The decision to use a particular test for a specific use case must be informed by clinical expert opinion at the time, considering the disease prevalence, risks, benefits and downstream consequences of testing. See Annex 2 for further discussion.
Clinical (diagnostic) Specificity	**≥99.9%** (with 95% two-sided confidence intervals entirely above 99%) At a prevalence of 1%, for every 100,000 tests done, 99 test results could be incorrectly positive.	**≥99.5%** (with 95% two-sided confidence intervals entirely above 97%) At a prevalence of 1%, for every 100,000 tests done, 495 test results could be incorrectly positive.	A minimum of **250** SARS-CoV-2 negative cases (per sample type) with **370** required to meet the desirable criteria, see “Clinical Performance Evaluation” section below. Repeated testing strategies should carefully consider the impact of false positives on the positive predictive value of the approach. Confirmation testing of positive results by PCR is recommended for most use cases, but is especially important for tests meeting the acceptable criteria only.
Clinical Performance Evaluation	Positive and negative cases should be recruited prospectively and consecutively or	When prevalence is low, or in emergency use situations (e.g. a surge in cases of a new variant of Concern	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.

	randomly from the target population (i.e people without symptoms) without prior knowledge of their disease status (e.g. single-gate design). Studies directly comparing a new assay to the current state of the art test would be advantageous. Test samples should be collected by the target user 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	(VoC)), case-control designs using clinical samples with viral load distributions (determined by PCR) generalisable to the target population may be necessary. 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 intended for self-testing must include an evaluation of the useability of the device by the intended user.	Testing of all claimed specimen types should be performed and details provided for collection 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).

	outbreaks (for tests to rule-out) should also be considered.		
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 COVID-19 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.	No clinically relevant cross reactivity to common seasonal respiratory pathogens. Minimal interference caused by common interferents at clinically relevant concentrations (dependant on sample type and analyte).	See annex 1 for list

		Demonstration of SARS-CoV-2 variant detection in silico and in vitro, where suitable reference materials are available.	
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 1000 SARS-CoV-2 RNA copies/mL of sample.	An appropriate unit of measurement for the target analyte (e.g. International Units) equivalent to a viral load of less than 1,000,000 SARS-CoV-2 RNA copies/mL of sample.	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 specific 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 RNA copies/mL, the quantity value and measurement uncertainty of the clinical samples used (or matched samples) should be assigned using an appropriate reference method (e.g. dPCR).

			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. Commercially available quality control materials may not be value assigned with sufficient accuracy to enable LoD evaluation.
Invalid rate (test failure rate)	No more than 0.1%	No more than 5%	Performance must be demonstrated in studies carried out in the intended population, setting and user groups when self-testing. This must take into account the skills and means of users and the influence resulting from variation that can reasonably be anticipated in users' technique and environment. The location, number and characteristics of participants involved must be reported and studies sufficiently powered. This must include pre (e.g. sampling) and post (e.g. reading) analytical errors in the relevant user groups. Inconclusive (indeterminate) results are not considered test failures, as long as they are correctly interpreted and acted upon by users. However, inconclusive results must be accounted for in estimates of clinical sensitivity and specificity, for further information refer to STARD 2015[4].
TEST PROCEDURE CHARACTERISTICS			
Number of steps to be performed by the operator	No more than 4 steps	5 or fewer steps	Steps to consider include • handwashing

			• collecting sample • applying sample • read results
Sample preparation	Limited sample preparation required. No more than 5 minutes.	No more than 15 minutes.	This refers to need to process sample prior to performing test.
Ease of Use	Very easy to use and interpret by the intended user. No need for additional equipment. Over 99% of participants must be able to complete the test procedure, read the result, interpret it correctly and understand the consequences.	Easy to use and interpret by the intended user. Over 95% of participants must be able to complete the test procedure, read the result, interpret it correctly and understand the consequences.	The design of the device should ensure that it is easy to use by the intended users without training at all stages of the procedure, and reduce as far as practicable the risk of use error in the handling of the device and in the interpretation of the results. This might include the use of effective risk communication aids, such as diagrams. Refer to WHO TSS1 requirements for self testing Part 3 Qualification of usability (self-testing)[2] and MHRA guidance on Human factors[3]. Conformity should be demonstrated from in-context usability and acceptability studies in the intended populations, users and environments. Evidence **must** be provided to show that users understand the test's intended use, limitations and do not misinterpret test results. This is especially important for "rule in" tests due to the high risk of misunderstanding and potential for misuse of tests to "rule out".
Requirement to add reagents e.g. sample diluent or buffer	None	Reagent provided in easy-to-use dispensing system	If a dropper bottle is used, WHO PQ Tech Guidance series 2 and its annex can be followed to establish stability.[2]

Time to result including sample acquisition and processing.	No more than 10 minutes	No more than 30 minutes	Conformity should be demonstrated from in-context usability and acceptability studies in the intended populations, users and environments.
Result	Results need to be expressed and presented in a way that is readily understood and correctly interpreted by a lay person.		Clear and appropriate information needs to be provided, with advice to the user on action to be taken (in case of positive, negative or inconclusive result) and on the possibility of false positive or false negative result. Evidence from usability studies should demonstrate that users have correctly interpreted and understood their result in line with Part IV of the UK MDR 2002, Annex I (as modified by Schedule 2A to the UK MDR 2002). Also refer to MHRA guidance on Human factors[3]. Manufacturers should demonstrate appropriate consideration of data protection issues. A digital readout or reader may aid user interpretation in some cases. Devices that simplify remote data captured electronically into a central data reporting system may be advantageous.
Biosafety	Design should mitigate need for special requirements to dispose test and the accessories needed to perform test No special biosafety measures should be required for self-testing		Instructions need to clearly identify risks of contamination and disposal requirements. Hazardous materials and handling of used test must comply with relevant regulations and not present a danger to the user or the environment. Any environmental requirements to prevent transmission (e.g. in the workplace) should be

			clearly indicated for the intended user in the instructions.
OPERATIONAL CHARACTERISTICS			
Test kit storage conditions	No cold storage ≤80% relative humidity	4 – 30 ^{0}C ≤70% relative humidity	
Operating conditions	0 - 40 ^{0}C ≤80% relative humidity	15 - 30 ^{0}C ≤70% relative humidity	Should it be reasonably foreseeable that the testing procedure may be undertaken outdoors, a lower temperature limit may be required.
Kit reagent stability	At least 6 months at 0 – 30 ^{0}C No cold chain required		Accelerated stability testing is acceptable provided it is supported by real time stability studies.
In use stability	More than 1 hour after opening of an individual pouch	More than 30 minutes after opening of an individual pouch	
Batch to Batch performance	Batches released should have equivalent sensitivity and specificity ranges.		Batch release criteria and methodology should be focused on the performance claims of the manufacturer, refer to WHO TGS-6 Panels for quality assurance and quality control of in vitro diagnostic medical devices[2] and BS EN 13975:2003 Sampling procedures used for acceptance testing of in vitro diagnostic medical devices.
Reagents reconstitution (need to prepare the reagents prior utilization)	None	All reagents, including water, already in kit	
End point stability (time window during which signal remains valid)	A minimum of 1 hour	A minimum of 20 minutes	
Disposal requirements	Dispose in household waste		If a containment bag is needed to enclose the device components, it must be provided. Disposal method must be safe and clear for incorporation in regular waste stream.

Kit presentation	Test components individually packed (if not single format). Include all required components and accessories to perform the test.		Consider the inclusion of an extra collection/sampling device
Training needs	No training needed.		
OTHER			
Environmental considerations	Environmental impact minimised through: the use of biodegradable materials in test cartridges, consumables and packaging; reducing excess packaging and where safe ensuring it can be recycled; and reducing environmentally harmful reagents.		
[1]Regulatory status	UKCA, CE UKNI or CE 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 guidance for manufacturers of COVID tests can be found here.
Design and manufacturing environment	Conforms to ISO 13485:2016 and ISO 14971:2019		
[1]Labelling and Instructions for Use (IFU)	In line with Part IV of the UK MDR 2002, Annex I (as modified by Schedule 2A to the UK MDR 2002). Simple interpretation by a lay person with pictorials to aid sampling and results interpretation and what to do with the test if the control fails. Clear reading time.		Certain components, including those used for sample collection, may be considered to be under the UK Medical Devices Regulations 2002 (SI 2002 No 618, as amended) (UK MDR 2002) and in such cases, the product should conform to the relevant sections of that regulation. Online instructional videos or other media may be helpful in increasing user confidence and competency, but should not exceed 10 minutes in length.

	Instructions for interpretation of different ranges of intensity. Clear warnings of limitations for use including frequency of testing and expected performance characteristics. Manufacturers of tests for "repeated testing" will need to provide instructions on: (a) how to interpret results from repeated testing (b) what to do if recommended inter-screen intervals are missed, and how to interpret results in these instances The information provided must include a statement clearly directing that the user should not take any decision of medical relevance without first consulting their medical practitioner. Paper IFU Consider the implications for users with protected characteristics under the Equality Act 2010. Ensure users know that if they are harmed or have a reaction they should report to the MHRA Yellow Card scheme	All information that is required by the user to correctly use and interpret the test must be provided in the IFU and use of external websites should be limited. Evidence demonstrating that the information and instructions provided by the manufacturer can be easily understood and applied by the user should be acquired. Refer to WHO TGS-5 Designing instructions for use for in vitro diagnostic medical devices[2]

Guidance

[1]In vitro diagnostic medical devices: guidance on legislation

[2] WHO - Technical Guidance Series (TGS) for WHO Prequalification – Diagnostic Assessment:

[3] Human_Factors_Medical_Devices.pdf (publishing.service.gov.uk)

[4] STARD 2015 guidelines for reporting diagnostic accuracy studies: explanation and elaboration - PubMed (nih.gov)

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 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 GISAID. 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 the Pfizer/BioNtech, AstraZeneca and Moderna COVID-19 vaccines 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 in respiratory/saliva specimens 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.

  - Mucin: bovine submaxillary gland, type I-S
  - Blood (human)
  - Nasal sprays or drops
  - Nasal corticosteroids
  - Nasal gel
  - Throat lozenges, oral anaesthetic and analgesic
  - Anti-viral drugs
  - Antibiotic, nasal ointment
  - Antibacterial, systemic
  - Human Anti-mouse Antibody (HAMA)
  - Biotin
  - Medications most often prescribed in the population for which the test is ordered
  - Common foods and drinks, including alcohol
  - Mouthwash and toothpaste

Post Market Performance considerations

An increase in the number of cases with new SARS-CoV-2 variants has been observed in the United Kingdom. The 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 new virus variant -202012/01 or other variants. Mutations are not exclusive to 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, the MHRA consider reports relating to Variants of Concern (VOC) to be serious public health threats, therefore significant safety issues should be reported within 48 hours.

Actions specific to new VOCs:

1. Inform the 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 the MHRA

Public visibility of device assurance

The MHRA intends 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 present 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	**1%**				
		SENSITIVITY					
			99.9%	97.0%	95%	80%	
SPECIFICITY		**Test Result**					
	99.9%	False Positives	990	990	990	990	
		False Negatives	10	300	500	2000	
	99.5%	False Positives	4950	4950	4950	4950	
		False Negatives	10	300	500	2000	

Numbers per		1000000	tested				
		Prevalence	**0.5%**				
		SENSITIVITY					
			99.9%	97.0%	95%	80%	
SPECIFICITY		**Test Result**					
	99.9%	False Positives	995	995	995	995	
		False Negatives	5	150	250	1000	
	99.5%	False Positives	4975	4975	4975	4975	
		False Negatives	5	150	250	1000	

Numbers per		1000000	tested				
		Prevalence	**0.1%**				
		SENSITIVITY					
			99.9%	97.0%	95%	80%	
SPECIFICITY		**Test Result**					
	99.9%	False Positives	999	999	999	999	
		False Negatives	1	30	50	200	
	99.5%	False Positives	4995	4995	4995	4995	
		False Negatives	1	30	50	200	

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 0.01% to 1% (1 in 10,000 to 1 in 100,000). Programmes and testing services should determine their own acceptance criteria, but illustrative desirable and acceptable thresholds of 75% and 50% PPV (1 in 4 and 1 in 2 positives are false positive) respectively and 0.001 and 0.01% 1-NPV (1 in 100,000 and 1 in 10,000 negatives are false negatives) are highlighted in green and amber respectively.

Desirable Rule In Test

Sensitivity	95%							
Specificity	99.9%							
Prevalence		***0.01%***	***0.02%***	***0.05%***	***0.10%***	***0.20%***	***0.50%***	***1.00%***
% +ves infected (PPV)		8.68%	15.97%	32.21%	48.74%	65.56%	82.68%	90.56%
% -ves infected (1-NPV)		0.0005%	0.0010%	0.0025%	0.0050%	0.0100%	0.0250%	0.0500%

Desirable Rule Out Test

Sensitivity	99.9%							
Specificity	99.9%							
Prevalence		***0.01%***	***0.02%***	***0.05%***	***0.10%***	***0.20%***	***0.50%***	***1.00%***
% +ves infected (PPV)		9.08%	16.66%	33.32%	50.00%	66.69%	83.39%	90.98%
% -ves infected (1-NPV)		0.0000%	0.0000%	0.0001%	0.0001%	0.0002%	0.0005%	0.0010%

Acceptable Rule In Test

Sensitivity	80%							
Specificity	99.5%							
Prevalence		***0.01%***	***0.02%***	***0.05%***	***0.10%***	***0.20%***	***0.50%***	***1.00%***
% +ves infected (PPV)		1.57%	3.10%	7.41%	13.81%	24.28%	44.57%	61.78%
% -ves infected (1-NPV)		0.002%	0.004%	0.010%	0.020%	0.040%	0.100%	0.201%

Acceptable Rule Out Test

Sensitivity	97%							
Specificity	99.5%							
Prevalence		***0.01%***	***0.02%***	***0.05%***	***0.10%***	***0.20%***	***0.50%***	***1.00%***
% +ves infected (PPV)		1.90%	3.74%	8.85%	16.26%	27.99%	49.36%	66.21%
% -ves infected (1-NPV)		0.000%	0.001%	0.002%	0.003%	0.006%	0.015%	0.030%

Annex 3 Glossary

BSL	Biological Safety Level
CL	Containment level
Ct	Cycle threshold
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: 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)