Medicines & Healthcare products Regulatory Agency

MHRA

TARGET PRODUCT PROFILE

Antibody tests to help determine if people have immunity to SARS-CoV-2

Issued by MHRA

Version Control

1.0		Initial document
2.0		Changes to specifications Changes to introduction

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 provide a common foundation for the development of tests that 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.

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 Pillar 3 of the UK testing strategy. How closely a product matches the TPP will be helpful in procurement and regulatory decision making. Any deviation from existing standards must be fully justified. Production lead time will also factor into decision making.

Implementation of Pillar 3 of the testing strategy relies on availability of simple antibody tests that could tell people whether they have had the virus and are now immune. Such tests require taking a small blood sample and looking for the presence of the neutralising antibodies specific to SARS-CoV-2, the causative agent of COVID-19. When available these tests would be used in community settings and eventually in the home. They should thus be simple, robust and have a rapid time to test result.

Antibody tests for other purposes are not part of this profile and might include:

- to determine if a symptomatic individual has a reasonable likelihood of a current infection
- to determine if an at-risk individual with or without symptoms in an endemic setting has a reasonable likelihood of a current infection
- to aid in the diagnosis of a symptomatic individual with a SARS CoV-2 infection
- to monitor a local or sentinel population in order to obtain early indications of a COVID-19 outbreak.

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 to those supporting use for Pillar 3. These TPPs are profiles based on our best information, but the science is rapidly evolving.

Clinical performance requirements

This is a specification of the clinically acceptable specifications for point of care and self-tests to be made and used in the UK during the current COVID-19 pandemic caused by SARS-CoV-2 virus. 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 Pillar 3 of 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 determine if an individual has previously been exposed to SARS-CoV-2 (and not other coronaviruses circulating in the population), and ultimately, if they are immune. As such, the test should detect IgG antibodies, specific to the virus and that are neutralising in their function.
As these tests are intended to be used in a community or home setting, they need to be simple and thus a lateral flow is likely to provide this solution.

The criteria for clinical specificity is set deliberately high in a test intended to detect immunity where the result may be given in the absence of a confirmatory test or without a known past PCR (Polymerase chain reaction) positive result. In a test with low specificity, there is an unacceptable risk that a person is incorrectly told that they are immune. They may consequently be exposed to infection and be at risk of illness and may also pass that infection on to others that they come in contact with. This is particularly a concern in people from a high-risk group, or a group which is directly exposed to vulnerable persons.

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. For instance, if it is proven that immunity is temporary and the antibody clears after a few months, it might be necessary to measure and monitor the antibody level and therefore the feature of a qualitative test may change to that for a quantitative of semi-quantitative test.

Antibody tests may be more useful in specific populations depending on the prevalence of antibodies. More work is needed before we can include targets for predictive values based on seroprevalence.

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.

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.

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

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TARGET PRODUCT PROFILE
COVID-19
SEROLOGY (ANTIBODY) POINT OF CARE TEST (POCT)[1] / NEAR PATIENT TEST (NPT)[2]

Key Feature	Desired	Acceptable	Comment
SCOPE			
Intended Use	To determine if an individual is immune to SARS-CoV-2	To determine if an individual has previously been exposed to SARS-CoV-2	Evidence for each intended use must include that which supports the specificity of the immune response to SARS-CoV-2 (acceptable feature) and if claim is of immunity (desired feature), that the antibodies detected are protective
Target Population	People who need to know that they are immune to SARS CoV	People who may have recovered from suspected or confirmed SARS CoV 2 infection or may have	

[1] Point of care test
An in vitro diagnostic medical device intended to be used by a healthcare professional outside of a laboratory in primary or secondary care environments

[2] Near Patient Test
An in vitro diagnostic medical device that is not intended for self-testing but is intended to be used outside of a laboratory environment.

		previously developed an asymptomatic infection	
Target user	The person trained in operating the test kit	Health care professionals	
Target Use Setting	Clinics, pharmacies, workplaces and other non-laboratory settings	Clinics, pharmacies, workplaces and other non-laboratory settings	
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 accessories needed to perform the assay and blood collection (e.g. lancets, swabs)	A standardised kit that contains all materials required for the procedure in a self-contained kit that includes reagents Accessories for specimen collection to be provided separately	
Target Analyte	IgG antibodies to SARS-CoV-2 virus	Total antibodies to SARS-CoV-2 virus	Assay design should use antigen known to be that which stimulates a specific response to the virus. The kinetics of the humoral response for COVID-19 are not yet fully understood but total antibody (IgA, IgM, and IgG) may be useful.
Sample type	Capillary whole blood from fingerstick sample OR	Capillary whole blood from fingerstick sample	Clinical sensitivity and specificity must be determined for each claimed

	Venous blood, serum or plasma		specimen type and anticoagulant. Sample equivalence must be shown.
Result Output	Qualitative		
Internal control	Included. Procedural flow control detecting the capability of the assay.		Controls that only detect migration of specimen are not considered sufficient.
Ease of Use	One signal test PLUS control Easily interpreted by the intended user No need for additional equipment to read result (eg camera, etc) Operator is able to record results without having to write them manually	One signal test PLUS control Easily interpreted by the intended user	
Identification capability	Labelling of the device with the patient/donor identification must be feasible		For a lateral flow test, this means the cartridge must have sufficient space for patient ID (either manually added or via a patient label)
Pack size	Single or multiple test kits		
Power requirements	None required		
Need for calibration/spare parts	None		
PERFORMANCE CHARACTERISTICS			

Clinical Sensitivity	Greater than 98% (with 95% confidence intervals of 96-100%) on specimens collected 20 days or more after the appearance of first symptoms.		These statistics rely on testing of at least 200 confirmed positive cases. See annex
Clinical Specificity	Greater than 98% (within 95% confidence intervals 96-100%)		These statistics rely on testing of at least 200 confirmed negative cases or from testing of specimens collected at least 6 months before the known appearance of the virus. See annex
Analytical Specificity	No known cross-reactivity with other known coronavirus, common respiratory pathogens	Minimal cross-reactivity with other known coronavirus, or common respiratory pathogens	Refer to list in Annex for relevant pathogens
Invalid rate	No more than 0.1%	No more than 1%	
TEST PROCEDURE CHARACTERISTICS			
Number of steps to be performed by the operator	No more than 4 steps,	No more than 5 steps	Steps to consider include • lance fingertip • apply blood • apply buffer • read
Sample preparation	Not required	No more than 15 minutes	Need to process sample prior to performing test
Need for operator to transfer a precise volume of sample or reagents	No	Acceptable if robust transfer device is provided with the test device and if variation	

		does not affect the test results	
Requirement to add reagents e.g. sample diluent or buffer	No	Reagent provided in a dropper bottle	
Time to result	No more than 15 minutes	No more than 20 minutes	
Result	Consists of easily reading and interpreting the results of the test and the control.		For a lateral flow test, this means that there will be two lines to read and interpret
Biosafety	No biosafety should be needed in addition to Personal Protective Equipment		
OPERATIONAL CHARACTERISTICS			
Test kit storage conditions	5 – 30 ^{0}C 80% relative humidity		
Operating conditions	15 - 25 ^{0}C 80% relative humidity		
Kit reagent stability	At least 12 months at 5 – 30 ^{0}C No cold chain is 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	
Reagents reconstitution (need to prepare the reagents prior to utilisation)	All reagents provided and ready to use	All liquids, including water, already in kit	
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.
Reader to reader variation	More than 95% of readers should detect true positive results near the limit of detection		
Volume of sample	Single drop for fingerstick tests	No more than two drops for fingerstick tests	
Disposal requirements	None, device and accessories should be disposed in standard biological waste containers, no glassware or be biodegradable or combustible	None, device and accessories should be disposed in standard biological waste containers	
Kit presentation (if not single format)	No greater than 100 tests Test components individually packed Accessories not too small to be used with regular examination gloves Include all required components and accessories to perform the test	5 Test kit Test components individually packed Accessories not too small to be used with regular examination gloves.	Kit presentation (if not single format)
Training needs (Time dedicated to training session for end users)	None Job aid included in test kit	Minimal Job aid included in test kit	Training needs Time dedicated to training session for end users.

			Job aids are summaries of all the operational steps in performing the test, usually pictorial in content.
OTHER			
Labelling and Instructions for Use	In accordance relevant requirements of Annex I of the IVD Directive (98/79/EC) Simple interpretation by lay person with pictorials to aid sampling and results interpretation and what to do with the test if the control fails Clear reading time Instructions for interpretation of different ranges of intensity Clear warnings of limitations for use including expected performance characteristics Paper or electronic		
Regulatory status	CE marked, or in process of meeting EU regulatory requirements for in vitro diagnostic medical devices		
Design and manufacturing environment	Conforms to ISO 13485:2016		

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TARGET PRODUCT PROFILE
COVID-19
SEROLOGY (ANTIBODY) SELF-TEST[3]

Key Feature	Desired	Acceptable	Comment
SCOPE			
Intended Use	To determine if an individual is immune to SARS-CoV-2	To determine if an individual has previously been exposed to SARS-CoV-2	Evidence for each intended use must include that which supports the specificity of the immune response to SARS-CoV-2 (acceptable feature) and if claim is of immunity (desired feature), that the antibodies detected are protective
Target Population	People who need to know that they are immune to SARS CoV	People who may have recovered from suspected or confirmed SARS CoV 2 infection or may have previously developed an asymptomatic infection	
Target user	A lay person with no knowledge of self-testing technology		
TEST DESIGN CHARACTERISTICS			

[3] Self-Test: An *in vitro* diagnostic medical device intended to be used by a lay person

Test format	A standardised kit that contains all materials required for the procedure in a self-contained kit that includes controls, reagents and accessories needed to perform the assay and blood collection (e.g. lancets, swabs)		
Target Analyte	IgG antibodies that neutralise SARS-CoV-2 virus	Total antibodies to SARS-CoV-2 virus	Assay design should use antigen known to be that which stimulates a specific response to the virus
Sample type	Capillary whole blood from fingerstick sample		Clinical sensitivity and specificity must be determined for each claimed specimen type and anticoagulant. Sample equivalence must be shown
Result Output	Qualitative		
Internal control	Included. Procedural flow control detecting the capability of the assay		Controls that only detect migration of specimen are not considered sufficient
Pack size	No more than 2 tests/kit	Single test kits	
Power requirements	None required		
Need for calibration/spare parts	None		
PERFORMANCE CHARACTERISTICS			
Clinical Sensitivity	Greater than 98% (with 95% confidence intervals of 96-100%) on specimens collected 20 days or more after the appearance of first symptoms.		These statistics rely on testing of at least 200 true positive cases.
Clinical Specificity	Greater than 98% (within 95% confidence intervals 96-100%)		These statistics rely on testing of at least 200 confirmed negative cases or

			from testing of specimens collected at least 6 months before the known appearance of the virus.
Analytical Specificity	No known cross-reactivity with other known coronavirus, common respiratory pathogens	Minimal cross-reactivity with other known coronavirus, or common respiratory pathogens	Refer to list in Annex for relevant pathogens
Invalid rate	No more than 0.1%	No more than 1%	
TEST PROCEDURE CHARACTERISTICS			
Number of steps to be performed by the operator	No more than 5 steps	No more than 6 steps	Steps to consider include • handwashing • lance fingertip • apply blood • read • apply plaster to fingerstick site
Sample preparation	Not required	No more than 15 minutes	Need to process sample prior to performing test.
Ease of use	One signal test PLUS control Easily interpreted by the intended user No need for additional equipment to read result (e.g. camera, etc)	One signal test PLUS control Easily interpreted by the intended user	

	Operator is able to record results without having to write them manually		
Need for operator to transfer a precise volume of sample or reagents	No	Acceptable if robust transfer device is provided with the test device and if variation does not affect the test results	
Requirement to add reagents e.g. sample diluent or buffer	No	Reagent provided in a dropper bottle	
Time to result	No more than 5 minutes	No more than 20 minutes	
Result	Consists of easily reading and interpreting the results of the test and the control		For a lateral flow test, this means that there will be two lines to read and interpret
Biosafety	No biosafety should be required for self-testing or disposal of test/lancet		
OPERATIONAL CHARACTERISTICS			
Test kit storage conditions	5 - 30 ^{0}C 80% relative humidity		
Operating conditions	15 - 25 ^{0}C 80% relative humidity	15 - 25 ^{0}C 70% relative humidity	
Kit reagent stability	At least 12 months at 2 - 35 ^{0}C No cold chain is 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	
Reagents reconstitution (Need to prepare the reagents prior utilisation)	All reagents provided and ready to use	All liquids, including water, already in kit	
End point stability (time window during which signal remains valid)	Up to 1 hour	Up to 30 minutes	
Reader to reader variation	More than 95% of people should detect true positive results near the limit of detection		
Volume of sample	Single drop for fingerstick tests	No more than two drops for fingerstick tests	
Disposal requirements	None, dispose in household waste		
Kit presentation (if not single format)	no greater than 2 tests Test components individually packed Accessories not too small to be used with regular examination gloves Include all required components and accessories to perform the test	Single test kit Test components individually packed Accessories not too small to be used with regular examination gloves	Kit presentation (if not single format)
Training needs (Time dedicated to training session for end users)	None Job aid included in test kit along with the IFU		Job aids are summaries of all the operational steps in performing the test, usually pictorial in content

OTHER		
Labelling and Instructions for Use	In accordance relevant requirements of Annex I of the IVD Directive (98/79/EC) Simple interpretation by lay person with pictorials to aid sampling and results interpretation and what to do with the test if the control fails Clear reading time Instructions for interpretation of different ranges of intensity Clear warnings of limitations for use including expected performance characteristics Paper	
Regulatory status	CE marked	
Design and Manufacturing environment	Conforms to ISO 13485:2016	

ANNEX: ASSAY VALIDATION

Establishing Performance Characteristics.

The following aspects should be considered when designing and validating the assay:

- When available, reference material should be used to establish performance, including seroconversion panels, quality control materials and proficiency testing materials.
- There is no currently agreed reference standard for establishing specimen immunity status. In the absence of such agreed position, it is recommended that a reference standard used for establishing truth is a composite standard, comprised of the following: “Appropriately timed specimens collected from symptomatic patients diagnosed in a laboratory with validated assays.” Technical documentation should include your rationale for your specimen characterisation and also any discrepant result analysis.
- When establishing analytical specificity, the following should be considered:
    - prepandemic samples,
    - other coronoavirus, 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)*

Other

Additional MHRA guidance “Guidance for Notified Bodies on the Regulation of Devices for Self-Testing” is a helpful resource to consider.