Medicines & Healthcare products Regulatory Agency

MHRA

TARGET PRODUCT PROFILE

Enzyme Immunoassay (EIA) Antibody tests to help determine if people have antibodies to SARS-CoV-2

Version Control

1.0		Initial document

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 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. The TPP assists the UK government in making decisions regarding central procurement of antibody tests and might also be used in local procurement decisions. 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 antibody tests that could tell people whether they have had the virus. Such tests usually require taking a blood sample and looking for the presence of antibodies specific to SARS-CoV-2, the causative agent of COVID-19.

A positive result from this test does not guarantee immunity to COVID-19 infection and may not indicate the infectious status of the person. A negative test does not guarantee no prior COVID-19 infection. Some people may not develop an antibody response.

Clinical performance requirements*

This is a specification of the clinically acceptable specifications for a laboratory Enzyme Immunoassay (EIA) test 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).

The criteria for clinical specificity is set deliberately high in a test intended to detect an antibody response where the result may be given in the absence of 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 have made an antibody response. 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.

Manufacturers claiming to have an assay intended to show clinical immunity, or that correlates with potential immune protection, must have scientific evidence to support the claim. They should also have made a risk assessment in line with ISO14971 for medical devices to address the intentional and unintentional use of the results of an antibody test.

It should be noted that a different TPP may be required for different case uses. Other future use cases may need to consider, for example, use of home collection of samples such as capillary blood or saliva with appropriate validation of performance and usability; or samples from hospitalised convalescent patients.

As such the contents of the TPPs in this document are restricted to those supporting use for Pillar 3. Failure to meet the criteria set out in the TPP does not necessarily mean that a test doesn't have wider applications for use in the UK*.
These TPPs are profiles based on our best information, but the science is rapidly evolving. The TPP is subject to review and may need to be updated at short notice.

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)
Enzyme Immunoassay (EIA) test

Key Feature	Desired	Acceptable	Comment
SCOPE			
Intended Use	To determine if an individual has made an antibody response to SARS-CoV-2		Each intended use must have evidence for scientific validity and include that which supports the specificity of the immune response to SARS-CoV-2 Assays intended to show an immune response that correlates with potential immune protection must either explicitly measure neutralising antibodies or measure binding antibodies that have a proven correlation with neutralising titre
Target Population	To determine possible immune protection against SARS-CoV-2.	People who may have recovered from suspected or confirmed SARS CoV-2 infection or may have previously developed an asymptomatic infection	

Target user	Laboratory trained Health care professionals		
Target Use Setting	Medical Laboratories working to appropriate quality & competence standards		e.g. ISO15189:2012
TEST DESIGN CHARACTERISTICS			
Test format	Either a) A kit containing all materials required for testing. This includes a standard, coated 96 well EIA plate, and all necessary reagents including, (as needed) specimen diluent, wash buffer, conjugate, substrate, acid, calibrators (if required) and controls and their requisite dilution material. OR b) A kit containing all lot specific material required for testing. This includes a standard, coated 96 well EIA plate, and all related lot-specific reagents such as conjugate and calibrators (if required). Supply of any non-lot specific material (eg controls, wash buffer, diluents, substrate and acid etc) provided separately.		Specimen collection requirements, unless specific to the assay, do not need to be addressed. Note: Assay may be automated. Multi-test formats other than 96 well EIA plates, using different technologies, may be useful.
Target Analyte	IgG Antibodies to the SARS-CoV-2 virus[i]	Total antibodies (IgG or IgA or IgM) to the SARS-CoV-2	Note: Design should incorporate a target which is correlated with previous infection or immune protection The kinetics of the humoral response for COVID-19 are not yet fully understood but total antibody (IgA, IgM, and

			IgG in any combination) may be useful
Sample type	Whole blood &/or plasma, &/or serum		If more than one sample type is specified clinical sensitivity and specificity must be determined for each claimed sample type
Result Output	Quantitative/ semi-quantitative	Qualitative	Where quantitation (full or semi) is the output, the interpretation of the result must be clear and linked, with evidence. Lot to lot precision must be considered in assigning any such quantitation. Note: International/National reference standards used when available
Assay controls	Controls that provide evidence that the IVD has functioned correctly – they must accurately monitor performance of the assay against the critical performance claims.		Assays compatible with external quality assessment schemes desirable
Identification capability	Ability to link patient/donor identification must be feasible		For plate format this must include identification system of wells or sample positions or possibility to barcode.
Pack size	Single or multiple test kits e.g. 96 wells EIA plates		
Need for calibration/spare parts	Calibrators and User serviceable spare parts should be available if required for the assay system		
PERFORMANCE CHARACTERISTICS			

Clinical Sensitivity	≥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. Note: See Introduction-Clinical performance requirements*
Clinical Specificity	≥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. Note: See Introduction-Clinical performance requirements*
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 Known Cross reactions should be listed in the IFU
TEST PROCEDURE CHARACTERISTICS			
Sample preparation	Some processing acceptable with standard laboratory equipment		Need to process sample prior to performing test appropriate to sample type. Appropriate containment environment must be specified.
Specimen volume in assay	5-50uL	5-50uL	Can be prediluted

Reagent volume per well	Volume of reagents to well (apart from wash) ≤100uL.	Volume of reagents to well (apart from wash) ≤100uL	Volumes apply to standard 96 well EIA plate formats.
Result	Comes with either easy manual calculations or a software programme for result calculations and monitoring of QC.		Specify requirements for the assay e.g. Plate reader, automated plate washer, spectrophotometer
Biosafety	No additional biosafety should be needed to use of standard medical laboratory practice.		
OPERATIONAL CHARACTERISTICS			
Test kit storage conditions	15 - 25 ^{0}C, 80% relative humidity	2 – 8 ^{0}C.	
Operating conditions	Either 15 - 25 ^{0}C or 37 ^{0}C for specimen and conjugate incubations.		
Kit reagent stability	At least 6 months at 2-8 ^{0}C or 12 months at -20^{0}C		Accelerated stability testing is acceptable provided it is supported by real time stability studies.
In use stability	All reagents (as presented) stable for up to 12 test runs over a period of a minimum of 3 months.		
End point stability (time window during which signal remains valid)	If not automated, ≥30 min		Fully automated system may read signal as part of the process
Disposal requirements	Device and accessories should be disposed in standard biological waste containers, no glassware Or be biodegradable or combustible.		
Training needs (Time dedicated to training session for end users)	For both: No special training requirements for laboratories familiar with performing routine manual or automated EIAs		

OTHER			
Result interpretation	Clear instructions for grey zones, interpretation of quantitative or semiquantitative results, including significance when comparing results taken in time sequence (i.e. comparing results taken on different days). Requirements for confirmation or repeat testing clearly described.		All result interpretation must be supported by evidence.
Instructions for Use (IFU)	In line with IVDD (98/79/EC) Annex 1 requirements Simple interpretation to aid sampling and results interpretation and what to do with the test if the control fails Clear reading time Instructions for results interpretation across reporting range Clear warnings of limitations for use including expected performance characteristic Paper or electronic		
Interferences	Interferents should be included in risk evaluation from endogenous and exogenous sources		See Annex for possible examples
Hook Effect	Assay design is such that potential for false results due to a hook effect is not an issue	Assays should specify their linear reporting range and upper limit of reporting.	Definition: The phenomenon whereby the effectiveness of antibodies/antigens to form immune complexes is sometimes impaired when concentrations of an antibody or an antigen are very high.
Regulatory status	CE marked, or in process of meeting EU regulatory requirements for in vitro diagnostic medical devices		

Design and Manufacturing environment	Conforms to: BS EN ISO 14971:2019 Medical devices. Application of risk management to medical devices ISO 13485:2016 Medical devices. Quality management systems, Requirements for regulatory purposes	
Labelling and IFU	In accordance with Annex I of the IVD Directive under essential requirements	Compliant with IVD Medical Device Directive

ANNEX: ASSAY VALIDATION

Establishing Performance Characteristics.

It is recommended that the following aspects are 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:
    - Pre-pandemic 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
    - Epstein–Barr virus (EBV)
    - Rubella IgM
    - *Chlamydia pneumoniae*
    - *Haemophilus influenzae*
    - *Legionella pneumophila*
    - *Mycobacterium tuberculosis*
    - *Streptococcus pneumoniae*
    - *Streptococcus pyogenes*
    - *Bordetella pertussis*
    - *Mycoplasma pneumoniae*
    - *Pneumocystis jirovecii (PJP)*

[#]specimens collected at least 6 months before the known appearance of the SARS-CoV-2 virus.

- Potential interferents may originate from the following endogenous and exogenous sources

  Endogenous substances

  •Haemoglobin

•Bilirubin
•Protein
•Triglycerides
•Rheumatoid Factor
•Total IgM
•Polyclonal hypergammaglobulinemia
•Hematocrit
•Antibodies developed against protein expression system used to generate recombinant antigens where relevant
• heterophiles

Exogenous substances

•Recommended anticoagulants e.g. EDTA

Other

Confirmation tests: consider reference laboratory PCR or reference serology algorithm