Medicines & Healthcare products Regulatory Agency

COVID-19 test approval
Step 2: Process for desktop review

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This guidance outlines how the government will undertake the desktop review of COVID-19 detection tests submitted for assessment under the Coronavirus Test Device Approvals (CTDA) Regulation. The Regulation requires manufacturers or distributors of molecular and antigen tests for COVID-19 to apply to the Medicine and Health products Regulatory Agency for approval to market their test in the UK, see COVID-19 test approval: how to apply.

Their product must meet the requirements of The Medical Devices (Coronavirus Test Device Approvals) (Amendment) Regulations 2021.
Please note, for multiplex products that have multiple detection targets, only the SARS-CoV-2 assay component will be assessed under CTDA Regulations as outlined in this guidance.

Molecular tests detect viral RNA or DNA and include Polymerase Chain Reaction (PCR), Isothermal Amplification and Loop-Mediated Isothermal Amplification (LAMP) tests. Antigen tests directly detect viral proteins or components of the virus other than nucleic acids and include those that require an analyser/reader and lateral flow tests that do not. All COVID-19 molecular and antigen tests are subject to approval, whether they are designed for use in a laboratory, at point of care, near patient or for home use (self-test).

Overview of the process

The desktop review is a systematic assessment of the evidence submitted by a supplier against a minimum set of requirements. The purpose of this step is to prevent tests that are below the expected standards from progressing to a technical validation in a laboratory. The information submitted will be reviewed to check for completeness and then passed to a Scientific Advisor who will undertake the initial assessment. The assessment will be peer reviewed and presented to the Desktop Review Assurance Group who will make a recommendation for pass/fail. All decisions will be ratified by the Regulatory Approvals Committee. The main areas of assessment are as follows:

1. Manufacturer and test information
2. Regulatory status
3. Intended Use Case
4. Test performance
5. Biosafety

1: Manufacturer and test information

As a minimum the applicant should supply a PDF document of the Instructions for Use (IFU) for the submitted test. This document will be required to demonstrate the submitted test aligns with the intended use and evidence the stated performance characteristics of the submitted test. Several supporting documents in addition to the IFU will also be required (see table below).

The submitted information will be assessed to ensure that the key documents for the application are present.
The applicant must inform CTDA at CTDA@mhra.gov.uk if they make any changes to submitted information whilst their application is being considered.

Supplementary documents uploaded with application	**Assessment**	**Response**
Current version of IFU (with date of publication). The IFU must contain all information on the validation and verification studies conducted to demonstrate the analytical and clinical performance of the assay, including target population, sample type and stability claims. The IFU must be written in English language.	Supplied/Not Supplied	Automatic reject if not supplied
IFU for all comparator assays that were used to evaluate performance characteristics	Supplied/Not Supplied	Automatic reject if not supplied
Biosafety documents (including viral inactivation where a claim of inactivation is stated in the IFU)	Not applicable/ Supplied/Not Supplied	Automatic reject if not supplied where applicable
Evidence of performance characteristics (see Section 4. Test performance for full details)	Supplied/Not Supplied	Automatic reject if not supplied Automatic reject if the comparator assay is not acceptable
Field safety notices (wherever issued) related to the submitted test issued from 01/01/2020 to date of application, and any pending notices.	Not applicable/Supplied/Not Supplied	SA to assess impact and resolution of issue
Regulatory certification (see Section 2. Regulatory status for acceptable certification)	Supplied/Not Supplied	Automatic reject if not supplied

2: Regulatory status

Acceptable regulatory status:

- UK(CA) Declaration of conformity
- CE Declaration of conformity and/or EU-type examination certificate
- For self-test devices, regulatory certificate must be issued from a UK Approved Body or EU Notified Body.

3: Intended Use Case

The IFU must outline the following information in the intended use statement.

Criteria	Documentation	Response	Guidance Notes
Intended use	Please attach and highlight relevant reference in IFU and publications[1]	Automatic reject if not supplied	Please describe the intended use case
Target population	Please attach and highlight relevant reference in IFU and publications	Automatic reject if not supplied	Please describe if the submitted test is intended for symptomatic and/or asymptomatic cases (i.e. people that are infected but do not display symptoms)
Sample collection type and requirements	Please attach and highlight relevant reference in IFU and publications	Automatic reject if not supplied	Please state the specifications and product reference numbers for collection devices (including swabs, media and containers) that have been validated for use with the submitted test
Target use setting	Please attach and highlight relevant reference in IFU and publications	Automatic reject if not supplied	Please state if the submitted test is intended for use at point of care, near patient testing and/or laboratory based
Target user	Please attach and highlight relevant reference in IFU and publications	Automatic reject if not supplied	Please state if the submitted test can be used by a trained healthcare professional; member of the allied health professions; trained lay-person and/or self-test

[1] Publications of interest are scientific or medical journal articles that have been peer reviewed prior to publication. Publications that have not been peer-reviewed are acceptable but should be labelled as non-peer reviewed.

4: Test performance

Minimum evidence to support performance claim:

Desirable	Essential
150 clinical “Positive” samples across the full dynamic range of viral loads 250 clinical “Negative” samples as determined by a comparator laboratory RT-qPCR	100 clinical “Positive” samples across the full dynamic range of viral loads 150 clinical “Negative” samples as determined by a comparator laboratory RT-qPCR

The essential and desirable numbers of samples apply to **each sample type**, for example: nasal, nasopharyngeal, throat and saliva, and **in each sample collection type**, for example: dry swab, eluted in buffer such as saline or UTM or VTM. Results for different sample type and collection type should not be aggregated. Approval will only be provided for sample types where sufficient data is provided for that sample type, and where that data demonstrates performance above the thresholds specified for the applicable technology type.
The clinical performance of the assessed product, for the purposes of the regulatory thresholds, must be assessed across the full dynamic range of viral loads (approximate to CT <25, 25 to 30, >30-35, >35).
The performance characteristics (analytical and clinical) stated in the IFU must match the data submitted for CTDA application.

Acceptable comparator assay

All comparator assays must satisfy the following performance requirements:

- CE or UK(CA)-marked
- Have a sensitivity of 97% or above with the lower 95% confidence interval at 93% or above, and a specificity of 99% or above with the lower 95% confidence interval at 97% or above. These clinical performance metrics must be demonstrated using at least 100 positive clinical samples and 150 negative clinical samples (as indicated on the IFU).
- A comparator that only detects the E-gene for SARS-CoV-2 will not be acceptable. If a comparator test includes the E-gene as a target among other targets for SARS-CoV-2, the data for the E-gene must be able to be discriminated or separated from the Ct values of the other targets.
- The above requirements apply individually to each sample type and sample collection type under assessment, not in aggregate.
- On occasions, when discordant results are observed between the applicant assay and the comparator assay, a third test may be used as a resolver assay. This resolver assay must also meet the requirements for an acceptable comparator assay. Otherwise, the data from the resolver assay will not be considered and only the primary comparator assay data will be used to assess the application.

A list of suitable comparator assays is available, and it is recommended that the comparator assay to be selected from this list. Where an alternate assay outside of this list is used in an application, the comparator will be assessed as a CDTA candidate assay prior to consideration as an acceptable comparator assay.

Clinical Performance

The IFU, relevant raw data and published supporting documents will be assessed for the following requirements for evidence of clinical performance.

Clinical performance data must be derived from clinical samples only. No result from contrived or diluted samples will be accepted.
If frozen clinical samples were used for performance evaluation, sufficient data demonstrating sample stability (freeze-thaw study) must be provided.

Criteria	Documentation	Response	Requirement
The comparator assay(s) name, test number and dated IFU version	Please attach and highlight relevant reference in IFU and publications	Automatic reject without IFU	The comparator assay(s) must meet the requirements outlined above in "Acceptable comparator assay"
Sample size of positive clinical samples	Please attach and highlight relevant reference in IFU and publications	Automatic reject if <100	Minimal acceptable number of samples is 100, desired number is greater than or equal to 150
Sample size for negative clinical samples	Please attach and highlight relevant reference in IFU and publications	Automatic reject is <150	Minimal acceptable number of samples is 150, desired number is greater than or equal to 250
CT or viral load values of positive samples obtained in the comparator assay(s) CT values or equivalent for the internal control in the comparator assay(s)	Please attach and highlight relevant reference in IFU and publications	Automatic reject without raw data	The CT or viral load of the positive clinical samples as measured using the comparator assay(s) should span the dynamic range of clinically meaningful viral loads. This means that positive samples should be from people with high, high-medium, low-medium and low viral load approximate to CT values <25, 25 to 30, >30-35, >35; with no less than 10% of samples in any one category and no more than 40% in the CT<25 category) and represent the target population that the test is intended to be used in (e.g. symptomatic only)

Please state the clinical sensitivity of the submitted test determined by comparison with the comparator assay(s) and provide raw data to evidence the performance across the dynamic range of the assay (approximate to CT <25, 25 to 30, >30-35, >35)		Automatic reject without raw data	This is the sensitivity of your test when compared to the comparator assay for ALL positive samples. Raw data of each test sample for the comparator assay and submitted test are required to assess the validity of claim. These samples should cover the dynamic range of clinically meaningful viral loads (i.e. should be from people with high, high-medium, low-medium and low viral load approximate to CT <25, 25 to 30, >30-35, >35; with no less than 10% of samples in any one category and no more than 40% in the CT<25 category)
Please state the clinical specificity of the submitted test and provide raw data to evidence the statement	Please attach and highlight relevant reference in IFU and publications	Automatic reject	This is the specificity of your test when compared to comparator assay for all negative samples. Raw data, at the per sample level, of the comparator assay and submitted test are required to assess the validity of claim
For molecular assays, please state the number of SARS-CoV-2 targets in the submitted test and which gene(s) they are associated with	Please attach and highlight relevant reference in IFU and publications	Automatic reject if information is not provided	This information is required to aid the assessment of your test

Analytical Performance

The IFU, relevant raw data and published supporting documents will be assessed for the following requirements for evidence of analytical performance.

Criteria	Documentation	Response	Requirement
Please state the Limit of Detection (LOD) of your submitted test preferably in copies per ml. Where IFU states another unit e.g. copies/reaction please translate to copies/ml where possible. For some tests other units may be applicable e.g. $TCID_{50}$/ml	Please attach and highlight relevant reference in IFU and publications	Automatic rejection if don't state a LOD	Please also include the materials and method used to determine the LOD (e.g., running a quantified standard against the comparator RT-qPCR)
Please confirm *in silico* (and where appropriate *in vitro*) testing exclusivity of the submitted test (for molecular tests only)	Please attach and highlight relevant reference in IFU and publications	Automatic rejection if not supplied	Please provide details of *in silico* tests for primer and probe sequences and any subsequent *in vitro* testing resulting from organisms with identified *in silico* homology
For molecular tests the applicant must provide evidence of regular *in silico* analysis against SARS-CoV-2 Variants of concern or under investigation data as published on gov.uk. During the period the application is being considered, the applicant must inform CTDA at CTDA@mhra.gov.uk within 48 hours of confirmation that a variant of concern (VOC) affects the assay target region/s by *in silico* analysis	Please attach *in silico* evidence for variants of concern	For information only	Please provide details of *in silico* tests for primer and probe sequences against variants of concern. These data are not a requirement but will aid the assessment of your test. Please note this is a requirement from the MHRA for all COVID-19 tests.

For antigen-based assays, please state the protein target(s) and region/s	Please attach protein target information	Automatically reject if not provided	Please provide details of your test design and target region(s) e.g. monoclonal, polyclonal, terminus and target protein.
In vitro or *in silico* cross reactivity with common respiratory targets	Please attach and highlight relevant reference in IFU and publications	Automatic rejection if not supplied	Please provide raw data of *in silico* or *in vitro* studies with clinical or contrived samples known to contain other respiratory viruses. Examples include commercial EQA and control panels
In vitro effect of common interferants	Please attach and highlight relevant reference in IFU and publications	Automatic rejection if not supplied	Please provide raw data of any interfering substances and their concentration, that have been tested in combination with the submitted test. Please see the relevant MHRA Target Product Profile for the submitted test for the required checklist of interfering substances.

Technology performance thresholds for approval under CTDA

The Medical Devices (Coronavirus Test Device Approvals) (Amendment) Regulations 2021 outlines the regulatory requirement for sensitivity and specificity level for each test type. Please refer to the regulation for definitions of sensitivity and specificity in relation to a coronavirus test device.

True positive results are those that have a positive result on both the test device and the comparator assay. False negative results are those that have a negative result on the test device and positive on the comparator assay.
True negative results are those that have a negative result on both the test device and the comparator assay. False positive results are those that have a positive result on the test device and a negative result on the comparator assay.

We will use the following formula[2] for calculating 95% confidence intervals:

$$Lower\ 95\%\ CI = \frac{A - B}{C} \times 100 \qquad Upper\ 95\%\ CI = \frac{A + B}{C} \times 100$$

where $A = 2r + 1.96^2$ $B = 1.96\sqrt{1.96^2 + 4r(1-p)}$ $C = 2(n + 1.96^2)$

r = number of true positives (for sensitivity) or
number of true negatives (for specificity)
n = number of positives on comparator RT-PCR (for sensitivity) or
number of negatives on the comparator RT-PCR (for specificity)
$p = r/n$ (i.e. sensitivity or specificity as a proportion)

When calculating the percentage sensitivity and specificity and 95% confidence intervals, we will round to the nearest 0.1% for comparison with the thresholds. For example, a test with a lower 95% confidence interval that rounds to 92.9% or 93.0% would fail against a threshold of 93%, as the requirement is that the lower 95% CI is entirely above 93%. For examples, see the table below.

Lower 95% CI	Rounded to the nearest 0.1%	If compared to a threshold of	Pass / Fail
92.85%	92.9%	93%	Fail
92.95%	93.0%	93%	Fail
93.03%	93.0%	93%	Fail
93.05%	93.1%	93%	Pass
93.15%	93.2%	93%	Pass

[2] Wilson E.B. (1927) Probable inference, the law of succession, and statistical inference. *Journal of the American Statistical Association* **22**: 209–212 https://doi.org/10.2307/2276774. As described in Altman D.G., Machin D., Bryant T.N. & Gardner M.J. (2000) *Statistics with Confidence*, 2nd edition. BMJ Books, London

5: Biosafety

Applicant must state the biosafety requirements of their submitted test.

Where the submitted assay includes the use of a reagent that claims to inactivate the virus, the manufacturer must be able to evidence effective inactivation according to the BSI safety standards and/or Public Health England Position statement on inactivation of SARS-Cov-2: Implications for laboratory testing.

The IFU and any supporting documents will be assessed for the following areas as evidence of biosafety.

Criteria	Documentation	Response	Requirement
Please state the biosafety containment requirements for the submitted test	Please attach and highlight relevant reference in IFU and publications	Automatic reject if not supplied	The biosafety of the submitted test will impact the use-case scenario in which the submitted test can be utilised
Does the submitted test include a viral inactivation step?	Please attach and highlight relevant reference in IFU and publications	Automatic reject if not supplied	Please highlight where this is claimed within the IFU
If yes, the applicant must provide documented efficacy evidence according to BSI standards	Please attach and highlight relevant reference in IFU and publications	Automatic reject if not supplied if answer above is yes	Viral inactivation claims must be demonstrated with raw data. Evaluation of the inactivation claims will be conducted against the BSI safety standards and/or position statement on the inactivation of SARS-CoV-2. This requires that an inactivation protocol demonstrates, at a minimum, a reduction of the initial viral titre of at least 4 log (to base 10). Equivalence to similar products is not acceptable. See Position statement on inactivation of SARS-Cov-2: Implications for laboratory testing And COVID-19: safe handling and processing for samples in laboratories
If your submission does not include inactivation of clinical samples, please confirm	Please attach and highlight relevant reference in IFU and publications	Automatic reject if not supplied	Please provide evidence of sample preparation and processing method, e.g. non-aerosol creating, need for full PPE to allow

whether the submitted test can be used outside of a laboratory setting			scientific advisor to assess this claim