FULL-FLEDGED PRODUCT REGISTRATION VALIDATION REQUIREMENTS FOR COVID-19 TESTS (*SELF-TESTS*)

Information on product registration submission requirements can be found in the following Guidances, published online at http://www.hsa.gov.sg/medical-devices/guidance-documents.

- "GN-18 Guidance on Preparation of a Product Registration Submission for In Vitro Diagnostic (IVD) Medical Devices using the ASEAN CSDT" under header Product Registration
- "TR-02 Contents of a Product Registration Submission for In-Vitro Diagnostic Medical Devices using the ASEAN CSDT" under header Technical Reference Documents

In addition to the requirements specified in the above Guidances, the following aspects of analytical performance and clinical evidence will also be relevant, for the respective diagnostic tests intended for pre-market submission.

Nucleic Acid Self-Tests

Pre-clinical Validation

- Analytical Sensitivity
  - Limit of Detection (LoD)
    - Probit Analysis to estimate the LoD *or*
    - Confirmation of the LoD concentration with at least 20 replicates
  - Inclusivity
    - *In silico* analysis on SARS-CoV-2 sequences published in the last 6 months on GISAID database
    - Relevant assessments and study reports, which evaluate the impact of new SARS-CoV-2 variants of concern on test kit performance. Otherwise, to provide details of manufacturer's plan to mitigate any risks arising from new SARS-CoV-2 variants of concern, including plans for any on-going or new future studies.

- Analytical Specificity
  - Wet testing cross-reactivity
    - Study on other human coronaviruses (SARS-CoV, MERS-CoV, Coronavirus OC43, Coronavirus NL63, Coronavirus 229E, and Coronavirus HKU1)
    - Study on other respiratory pathogens (e.g. Influenza A virus (H1N1, H3N2), Influenza B virus, Respiratory Syncytial Virus (RSV), Adenovirus)
  - *In silico* cross-reactivity
    - BLAST analysis on the primers/probe
  - Interference
    - Endogenous substances, including but not limited to, mucin and blood for direct swabs
    - Exogenous substances (e.g. drugs), if any

    For interference, testing must be conducted on both positive and negative samples.

- Precision
  - Repeatability/Reproducibility (refer to CLSI EP05-A3)

- Linearity/ Measuring Range
  - For quantitative assays

- Cut off Values (as applicable)

- Sample Matrix Validation
  - Analytical study using contrived specimens on the claimed respiratory specimen type *or*
  - Clinical studies for all other patient sample types (e.g. saliva, oral fluids)

  For respiratory specimen types, studies performed on the most challenging specimen types (e.g. sputum) can be used to cover other matrices.

- Swab Equivalency
  - Where there are different swabs (e.g. different swab suppliers) that are to be supplied with the kit, equivalency study across the different swabs should be provided to validate that the performance of the assay is not affected by the different swabs.

- Stability Studies
  - Real time or accelerated aging studies on 3 lots of reagent
  - In-use stability studies (e.g. Freeze/Thaw) and onboard stability studies, if applicable, on 1 lot of reagent

Initial establishment of shelf-life can be based on the data from experience gained with IVD reagents that can reasonably be expected to be comparable with regard to their stability characteristics. (*ref ISO 23640*). However, the claim shall be verified with real time study data.

- Reading Time and Sample Volume Validation Studies

- Usability studies

Clinical Validation

- Structured Clinical Study
  - Designed to provide reasonable assurance of clinical performance.
    For detailed requirements, refer to TR-02 Contents of a Product Registration Submission for In Vitro Diagnostic Medical Devices using the ASEAN CSDT.
  - Method of determining clinical status of patients, whose samples will be used to determine sensitivity and specificity, must be consistent
  - Objective analysis of results and overall study conclusion provided
  - Clinical samples ideally should be sourced from a minimum of 2 sites
  - Prospective clinical study design is required

- Clinical Sensitivity
  - ≥ 95% for respiratory and saliva sample types (applicable after resolution of discrepant results)

- Clinical Specificity
  - 99% for respiratory and saliva sample types (applicable after resolution of discrepant results)

- Clinical Study Sample Size
    - For detection of SARS-CoV-2 infection, 300 positive samples from lay users should be tested for each claimed sample type, including non-respiratory specimen types such as saliva.
    - At least 50% of the positive samples should include samples from asymptomatic individuals.
    - 500 confirmed negative patient samples from lay users should be tested for each sample type.

- Clinical Study Comparator
  Any of the following criteria can be applied:
  - Comparison against actual clinical diagnosis, with clear criteria that defines confirmatory clinical diagnosis for the study patient
  - Method comparison done with an established PCR (e.g. listed on Singapore Medical Device Register). Comparator test(s) used should be clearly identified. Clinical testing laboratory which runs the comparator test should meet at least one of the following criteria:
    - Evidence that clinical lab is a national or country equivalent reference lab (e.g. certified by country's Ministry of Health or Competent Authority to conduct COVID-19 testing)
    - Possess ISO 15189 or CAP accreditation
    - [For SG labs] Listed on MOH's list of approved COVID-19 testing labs (*https://www.moh.gov.sg/licensing-and-regulation/regulations-guidelines-and-circulars/details/list-of-healthcare-institutions-approved-to-provide-sars-cov-2-polymerase-chain-reaction-(pcr)-testing-for-covid-19*)

Antigen Rapid Self-Tests

Pre-clinical Validation

- Analytical Sensitivity
  - For qualitative assays
    - Limit of Detection (LoD)
  - Inclusivity
    - Relevant assessments and study reports, which evaluate the impact of new SARS-CoV-2 variants of concern on test kit performance. Otherwise, to provide details of manufacturer's plan to mitigate any risks arising from new SARS-CoV-2 variants of concern, including plans for any on-going or new future studies.
    - Wet lab testing using recombinant protein for Delta and Omicron Variants of Concern is required. Testing should be conducted close to Limit of Detection (e.g. within 3x LoD, clinical samples with high Ct values).

- Analytical Specificity
  - Cross-reactivity
    - Studies on other human coronaviruses (SARS-CoV1, MERS-CoV, Coronavirus OC43, Coronavirus NL63, Coronavirus 229E, and Coronavirus HKU1)
    - Studies on other respiratory pathogens (e.g.: Influenza A virus (H1N1, H3N2), Influenza B virus, Respiratory Syncytial Virus (RSV), Adenovirus)
  - Interference
    - Endogenous substances, including but not limited to, mucin and blood for direct swabs
    - Exogenous substances (e.g. drugs), if any

    Testing must be conducted on both positive and negative samples.

- Precision
  - Repeatability/Reproducibility (refer to CLSI EP05-A3)

- High Dose Hook Effect
  - Studies conducted on samples with high antigen titres

- Cut off values (as applicable)

- Sample Matrix Validation
  - Analytical study using contrived specimens on the claimed respiratory specimen type *or*
  - Clinical studies for all other patient sample types (e.g. saliva, oral fluids, anal swabs)

  For respiratory specimen types, studies performed on the most challenging specimen types (e.g. sputum) can be used to cover other matrices.

- Swab Equivalency
  - Where there are different swabs (e.g. different swab suppliers) that are to be supplied with the kit, equivalency study across the different swabs should be provided to validate that the performance of the assay is not affected by the different swabs.

- Specimen Stability Studies

- Stability Studies
  - Real time or accelerated aging studies on 3 lots of reagent
  - In-use stability studies (e.g. open pouch), if applicable, on 1 lot of reagent

  Initial establishment of shelf-life can be based on the data from experience gained with IVD reagents that can reasonably be expected to be comparable with regard to their stability characteristics. (*ref ISO 23640*). However, the claim shall be verified with real time study data.

- Reading Time and Sample Volume Validation Studies

- Usability studies

Clinical Validation

- Structured Clinical Study
  - Designed to provide reasonable assurance of clinical performance.
    For detailed requirements, refer to TR-02 Contents of a Product Registration Submission for In Vitro Diagnostic Medical Devices using the ASEAN CSDT.

- Method of determining clinical status of patients, whose samples will be used to determine sensitivity and specificity, must be consistent
- Objective analysis of results and overall study conclusion provided
- Clinical samples should be sourced from a minimum of 2 sites
- Prospective clinical design study is required

- Clinical Sensitivity
  - ~ 90%
    Clinical performance data, stratified by days or duration post-symptom onset and Ct values, should be provided

- Clinical Specificity
  - 99%

- Clinical samples
  - 300 positive samples from lay users should be tested for each claimed sample type.
  - At least 50% of the positive samples should include samples from asymptomatic individuals.
  - 1000 confirmed negative patient samples from lay users should be tested, including within ~100 symptomatic PCR negative patients with no exposure to SARS-CoV-2.
    Alternatively, a comprehensive cross-reactivity study against other respiratory viruses may be considered in place of symptomatic PCR negative patient samples.

- Clinical Study Comparator
  Any of the following criteria can be applied:
  - Comparison against actual clinical diagnosis, with clear criteria that defines confirmatory clinical diagnosis for the study patient
  - Method comparison done with an established PCR or antigen test (e.g. listed on Singapore Medical Device Register). Comparator test(s) used should be clearly identified. Clinical testing laboratory which runs the comparator test should meet at least one of the following criteria.
    - Evidence that clinical lab is a national or country equivalent reference lab (e.g. certified by country's Ministry of Health or competent authority to conduct COVID-19 testing)
    - Possess ISO 15189 or CAP accreditation
    - [For SG labs] Listed on MOH's list of approved COVID-19 testing labs (https://www.moh.gov.sg/licensing-and-regulation/regulations-guidelines-and-circulars/details/list-of-healthcare-institutions-approved-to-provide-sars-cov-2-polymerase-chain-reaction-(pcr)-testing-for-covid-19)

- Additional Clinical Requirements
  - Clinical performance data on current circulating variants (i.e. Omicron) should be provided. A minimum of 50 circulating variant positive sample, with at least 20% of them having high PCR Ct values (≥25), are to be tested.

Bridging from Professional-Use-Only Antigen Rapid Tests to Antigen Rapid Self-Tests

Add on clinical data requirements, for manufacturers seeking to develop non-PUO test kits through use of their existing PUO test kit (with PUO validation data) as a base.

- Labels must clearly indicate the test is intended for use by lay users (non-medical professionals).
- Minimum clinical sensitivity of ~ 90% when compared to PCR
- 200 positive and 400 negative samples, all prospectively collected, should be obtained from lay users. Data collected should cover full scope of self-use by lay user, including self-collection of sample and results interpretation. The sensitivity and specificity of the device for self-testing in the hands of the lay user shall be defined against the confirmed patient infection status.
- At least 150 positive samples should come from asymptomatic individuals.
- Clinical performance data on current circulating variants (i.e. Omicron) should be provided. A minimum of 50 circulating variant positive sample, with at least 20% of them having high PCR Ct values (≥25), are to be tested.