J Chin Med Assoc

REVIEW ARTICLE

The requirements of nucleic acid test for COVID-19 during public health emergency: Current regulatory in Taiwan, Singapore, and the United States

Yin-Ting Fan[a], Jin-Yu Lee[b], Yu-Che Cheng[b], Hsin-Hui Lin[b], Chia-Hung Chien[b], Pei-Weng Tu[b], Hui-Wen Chung[a,*]

[a]Office of Medical Device Evaluation, Center for Measurement Standards, Industrial Technology Research Institute, Hsinchu, Taiwan, ROC; [b]Division of Medical Devices and Cosmetics, Food and Drug Administration, Ministry of Health and Welfare, Taipei, Taiwan, ROC.

Abstract

In mid-2022, the COVID-19 cases have reached close to 562 million, but its overall infection rate is hard to confirm. Even with effective vaccines, break-through infections with new variants occur, and safe and reliable testing still plays a critical role in isolation of infected individuals and in control of an outbreak of a COVID-19 pandemic. In response to this urgent need, the diagnostic tests for COVID-19 are rapidly evolving and improving these days. The health authorities of many countries issued requirements for detecting SARS-CoV-2 diagnosis tests during the pandemic and have timely access to these tests to ensure safety and effectiveness. In this study, we compared the requirements of EUA in Taiwan, Singapore, and the United States. For the performance evaluations of nucleic acid extraction, inclusivity, limit of detection (LoD), cross-reactivity, interference, cutoff, and stability, the requirements are similar in the three countries. The use of natural clinical specimens is needed for clinical evaluation in Taiwan and the United States. However, carry-over and cross-contamination studies can be exempted in Taiwan and the United States but are required in Singapore. This review outlines requirements and insight to guide the test developers on the development of IVDs. Considering the rapidly evolving viruses and severe pandemic of COVID-19, timely and accurate diagnostic testing is imperative to the management of diseases. As noted above, the performance requirements for SARS-CoV-2 nucleic acid tests are similar between Taiwan, Singapore and the United States. The differences are mainly in two points: the recommended microorganisms for cross-reactivity study, and the specimen requirement for clinical evaluation. This study provides an overview of current requirements of SARS-CoV-2 nucleic acid tests in Taiwan, Singapore, and the United States.

Keywords: COVID-19; Emergency use approval (EUA); Nucleic acid tests; Regulation; SARS-CoV-2

1. OVERVIEW OF CORONAVIRUS AND CORONAVIRUS DISEASE-2019 TEST

The coronavirus is a single-stranded, positive-sense RNA virus, which belongs to the Coronaviridae family. The crown-shaped virus is 80 to 160 nm in size with its RNA genome size ranges between 27 and 32 K bp characteristically.[1,2] The viral envelope contains four major structural proteins: spike glycoprotein (S), membrane glycoprotein (M), and envelope small membrane protein (E), and the nucleocapsid phosphoprotein (N) that assists with viral RNA packaging. Due to transcription errors and RNA-dependent RNA polymerase (RdRP) jumps,[1,3] the coronavirus has a high recombination rate and mutation frequency.[3,4] The cross-species transmission and high contagion and mutation rate of coronavirus thus make the disease control and prevention especially difficult. The newly discovered SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) has resulted in confirmed cases in at least 190 counties since late 2019. According to the Communicable Disease Control Act, Taiwan also classified COVID-19 as a category 5 communicable disease on 15 January, 2020 to strengthen surveillance and containment of COVID-19.[5]

Correct diagnosis is the first line of defense against an epidemic. Clinical diagnosis of COVID-19 is hard, since it shares many symptoms with seasonal influenza at the early stage. It is pivotal to distinguish COVID-19 from the influenza virus as mistreatment and delay in quarantine can lead to super-spreading events.[6] At present, the diagnostic test for COVID-19 includes nucleic acid, antigen, and antibody tests (Table 1) with each of its own advantages and shortfalls.[7] Polymerase chain reaction (PCR) for nucleic acid detection is the primary choice

* *Address correspondence. Dr. Hui-Wen Chung, Office of Medical Device Evaluation, Center for Measurement Standards, Industrial Technology Research Institute, 321, Section 2, Kuang-Fu Road, Hsinchu 300, Taiwan, ROC. E-mail address: huiwen@itri.org.tw (H.-W. Chung).*

Conflicts of interest: The authors declare that they have no conflicts of interest related to the subject matter or materials discussed in this article.

Journal of Chinese Medical Association. (2022) 85: 1038-1043.

Received January 27, 2022; accepted July 25, 2022.

doi: 10.1097/JCMA.0000000000000804.

Table 1

Comparison of COVID-19 test methods

	Common Specimens Collecting Sites	Test Duration	Quantitative/ Qualitative Analysis	Advantages	Disadvantages
Real-time RT-PCR	Nasopharynx, throat, lower respiratory tract	2 hours[a]	Qualitative	(1) High accuracy. (2) Well-established.	(1) Requires RNA extraction from specimens. (2) Requires special instruments. (3) The operation process is cumbersome.
Loop-mediated isothermal amplification (RT-LAMP)	Nasopharynx, throat, lower respiratory tract	1 hour	Qualitative	(1) Portable test. (2) High accuracy. (3) Naked eye observation.	(1) Requires water bath tank or heating plateof 60~65 ºC. (2) The operation process is cumbersome.
Rapid viral antibody test	Plasma, serum	15 minutes	Qualitative	(1) Can be operated at the specimens collecting site with safety and convenience. (2) The use of blood specimens reduces the splash and splatter risk of healthcare providers from patients.	Not applicable to the earliest diagnosis of disease.
Rapid viral antigen test	Nasopharynx, throat, lower respiratory tract	15 minutes	Qualitative	Can be operated at the specimens collecting site with efficiency and convenience.	Low accuracy

[a]Specimens shipping and processing time not included.

for diagnosing coronaviruses in humans. The viral nucleic acids from respiratory tract specimen of patients are amplified using RT-PCR and can be detected by fluorescent probes in 2 hours. Recently, reverse transcriptional loop-mediated isothermal amplification (RT-LAMP) has come to light.[8] This technique shortens the time required for conventional RT-PCR. However, both RT-PCR and RT-LAMP involve professionals and specific instruments. Rapid tests using antigen or antibody detection allow easy operation without specific instruments and quick access to diagnosis in 15 minutes.[9]

Serological tests are designed to detect the specific antibodies against viral proteins after infection. Once in contact with the virus, plasma cells are differentiated during incubation period before secreting antibodies, which last a longer time in circulation. However, rapid antigen screening test for COVID-19 allows quick detection and quarantine of potential carriers.

2. REGULATION OF EMERGENCY USE APPROVAL AROUND THE WORLD

The rapidly increased demand for medical devices and diagnostic tests resulted from the COVID-19 pandemic is generally governed under the existing regulatory framework in most health authorities worldwide. Emergency use approval is granted to medical devices including SARS-CoV-2 *in vitro* diagnostic (IVD) tests, masks, respirators, personal protective equipment, and so on. The health authorities in China, Korea, Taiwan, Singapore, and the United States have announced the provisional document or guidance of performance requirements for SARS-CoV-2 nucleic acid test. China and Korea have released a guidance for SARS-CoV-2 nucleic acid tests for regular premarket review, titled "Key Points of Technical Review for the Registration of 2019 Novel Coronavirus Nucleic Acid Detection Reagent" (China) and "Guidelines on the Review and Approval of *In Vitro* Diagnostic Medical Devices for COVID-19" (Korea).

However, some countries adopted temporary requirements for emergency use, such as Special Manufacturing Approvals: Nucleic Acid Tests for SARS-CoV-2 (Taiwan) and Policy for Coronavirus Disease-2019 Tests During the Public Health Emergency and the related Templates (United States). In addition, Singapore adopted temporary requirements for emergency use: provisional authorization of COVID-19 diagnostic tests—key validation requirements (Singapore) until 1 June, 2021 (Table 2).[10-18]

3. TAIWAN: SPECIAL MANUFACTURING APPROVALS—NUCLEIC ACID TESTS FOR SARS-COV-2

The Special Manufacturing Approval: Nucleic Acid Tests for SARS-CoV-2 was first issued on 24 March, 2020, by Taiwan Food and Drug Administration (TFDA) with the latest amendment made on 16 November, 2021.[12] The following documents are required for the special manufacturing approval: (1) Labeling of the device. (2) Device descriptive information as those requirements for regular approval, including the intended use, a general description of the principle of the assay method, target gene, and sequence characteristics, the composition and concentration of the primers, probes and control materials, a description of the specimen collection, and transport or storage materials provided with the device or recommended for use, a description of the appropriate instrumentation characteristics, a description or complete list of the various configurations/variants of the device, a description of the accessories and other products, which are intended to be used in combination with the device, interpretation of results and other precautions, limitation of the assay. (3) Product manufacturing quality system documentation. (4) Performance evaluation report which should at least include method of nucleic acid extraction and purification, inclusivity, cross-reactivity, interference, limit of detection, stability, and method comparison.

TFDA offers flexibility on performance requirements based on current situation and risk evaluation, for example, cross-reactivity evaluation of most pathogens can be replaced with results from database comparison. Limit of detection and method comparison of the test can also be evaluated using contrived specimens. Other information can also be waived under certain premises. The nucleic acid extraction and purification evaluation report can be justified with pre-existing laboratory SOP and affidavits. In addition, some data required in regular approval processes including cutoff, precision, carry-over and cross-contamination studies, specimen storage, and shipping are not needed.[12]

Table 2

Provisional document/guidance related to SARS-CoV-2 nucleic acid tests issued by the health authorities in Taiwan, Singapore, and the United States

Country	Document Types	Document/Guidance
Taiwan	Emergency use	• Special manufacturing approvals: nucleic acid tests for SARS-CoV-2. • Special manufacturing approvals: evaluation report for multitargeted nucleic acid test of SARS-CoV-2 and influenza virus.
Singapore	Emergency use	• HSA expedited approval of COVID-19 diagnostic tests in Singapore via provisional authorization. • Provisional authorization of COVID-19 diagnostic tests—key validation requirements.
The United States	Emergency use	• Policy for coronavirus disease-2019 tests during the public health emergency. • Molecular diagnostic template. • Supplemental template for molecular and antigen diagnostic COVID-19 tests for screening with serial testing.

4. SINGAPORE: PROVISIONAL AUTHORIZATION OF COVID-19 DIAGNOSTIC TESTS—KEY VALIDATION REQUIREMENTS

The Singapore Health Sciences Authority (HSA) issued Provisional Authorization for expedited approval of COVID-19 diagnostic tests in May 2020, and it changed to premarket review requirements from 1 June, 2021.[13,14] HSA still can determine a clinical need for the use of emergency medical devices,[15] and the previous emergency requirements can be used for reference.

While labeling and the brief description of the test are required when applying for provisional authorization for SARS-CoV-2 molecular diagnostic tests, a summary of analytical validation and clinical data and any planned or ongoing validation including clinical studies are also essential for application. Comparison with the performance evaluation required by TFDA, the Singapore HSA demands a report of usability test (for PoCT). The clinical evaluation study is not mandatory for the emergency approval process, the inclusivity, and cross-reactivity study can also be justified with the database comparison results. Moreover, sample matrix and nucleic acid extraction system validation can be conducted using contrived specimens on the most challenging specimen types (eg, sputum) for covering other claimed specimen types. To avoid cross-contamination between positive and negative results, verification of the LoD sample on the different instruments with at least 20 replicates is required.[13,14]

5. UNITED STATES: POLICY FOR CORONAVIRUS DISEASE-2019 TESTS DURING THE PUBLIC HEALTH EMERGENCY

On February 29, 2020, the US Food and Drug Administration (FDA) issued an immediately in effect guidance with policy specific to development of *IVD* tests during this public health emergency.[16-18] The latest version of this guidance was issued on November 15, 2021. The FDA also updates "template" irregularly to provide the FDA's current recommendations concerning what data and information should be submitted to the FDA in support of an Emergency Use Authorization (EUA) submission for SARS-CoV-2 molecular diagnostic assay. The required information for an EUA from the US FDA are generally similar to that from the TFDA. The product manufacturing information includes an overview of manufacturing and distribution, components included with the test or components required but not included with the test, software validation, testing capabilities, reagent, and sample stability. The performance evaluation information includes limit of detection, inclusivity, cross-reactivity and clinical evaluation.

The US FDA accepts some exemptions as well. *In silico* analysis can be used for assessing cross-reactivity if the pathogens are difficult to obtain, such as the SARS-Coronavirus, MERS-Coronavirus. If multiple clinical matrices are intended for clinical testing, the results from the most challenging matrix of each claimed clinical matrix type should be submitted in the documentation of limit of detection. Although contrived specimens are allowed in method comparison, FDA recommends that developers use positive clinical samples for clinical validation as the availability of positive samples has increased due to the progression of the pandemic. With the continuance of the pandemic and emergence of virus variants, FDA also suggested keeping monitoring the basis of mutations and variant on the test.[16-18]

6. SIMILARITIES AND DIFFERENCES OF REQUIREMENTS FOR SARS-COV-2 NUCLEIC ACID TEST BETWEEN TAIWAN, SINGAPORE, AND THE UNITED STATES

The overall requirements for SARS-CoV-2 nucleic acid test in Taiwan, USA, and Singapore are shown in Tables 3–5. The performance evaluation requirements on nucleic acid extraction, inclusivity, limit of detection (LoD), cross-reactivity, interference, cutoff, stability, and so on, are similar with a slight difference among Taiwan, Singapore, and United States. For example, LoD is acceptable for using a contrived specimen in Taiwan and United States, but it is not suggested specifically in Singapore.[13] However, it is clear that the LoD should be confirmed by using at least 20 replicates and at least 95% of replicates must be positive for all three. In addition, it is necessary to evaluate the performance of cross-reactivity in Taiwan, Singapore, and the United States, but the recommended list of microorganisms is not exactly the same. *In silico* analyses alone may be acceptable for SARS-CoV and MERS-CoV in Taiwan due to its difficulty in obtaining them, whereas the wet lab testing report should also be provided in the United States and Singapore. It is also suggested that assessments with the remaining pathogens assessment replaced by database comparison results should be performed at least for human coronavirus OC43, human coronavirus NL63, human coronavirus 229E, influenza A/B, adenovirus, respiratory syncytial virus, rhinovirus, parainfluenza in Taiwan.[12,17]

The United States also has a different recommended lists of high-priority organisms present for respiratory and saliva

Table 3

Comparison of the basic requirements for emergency use approval of SARS-CoV-2 nucleic acid tests between Taiwan, Singapore, and the United States

	Labeling	Device Descriptive Information	Product Manufacturing, Quality System Documentation
Taiwan	Required	Required	Required
Singapore	Required	Required	Required
The U.S.	Required	Required	Required

Table 4

Comparison of the requirements of performance evaluation for emergency use approval of SARS-CoV-2 nucleic acid tests between Taiwan, Singapore, and the United States

	Nucleic Acid Extraction	Controls	Inclusivity	Limit of Detection	Cross-reactivity	Interference	Cutoff	Precision	Carry-over and cross-contamination studies
Taiwan	Conditional exemption	(1) Blank (2) Negative (3) Positive (4) Internal (5) Human specimen	(1) *In silico* analysis. (2) All mutations.	(1) Contrived specimens. (2) At least 20 replicates. (3) Greater or equal to 95% positive results.	(1) Recommen-ded 40 organisms. (2) Wet lab testing. (3) *In silico* analysis.	Conditional exemption	Conditional exemption	Exemption	Exemption
Singapore	Conditional exemption	Exemption	Same as above (1)	Same as above (1)(2)(3)	(1) Recommen-ded 12 organisms.	Conditional exemption	Exemption	Required	Verify LoD with at least 20 replicates.
The U.S.	Exemption	Same as Taiwan (1)-(5)	Same as above (1)(2)	Same as above (1)(2)(3)	(1) Recommen-ded 6 organisms for all specimens. (2) Recommen-ded 21 organism for all respiratory specimens. (3) Recommen-ded 21 organism for salivaspeci-mens. (4) Wet lab testing. (5) *In silico* analysis.	Conditional exemption	Exemption	Exemption	Exemption

Conditional exemption: For interference study, it depends on the matrix that is indicated for the candidate test. If the extraction methods are previously reviewed or regularly used in the clinical laboratory, the test can be exempted.

specimens in cross-reactivity. For both types of specimens, the requirement of high-priority pathogens from the same genetic family is the same, including human coronavirus 229E, human coronavirus OC43, human coronavirus HKU1, human coronavirus NL63, SARS-CoV-1, MERS-coronavirus. In the guidance for both Taiwan and the United States, it mentioned that if the primer/probe sequences used consist ≥80% homology to the pathogen gene sequences on the list, choose one of the following methods: (1) conduct cross-reactivity analyses on those pathogens with ≥80% sequence homology. (2) Provide justification as to why the test performance would not be impacted by the presence of a causative agent of a clinically significant coinfection (eg, the quantity of primer/probe in Master mix).[12,17]

For clinical evaluation, both Taiwan and the United States require at least 30 positive and 30 negative natural clinical specimens should be tested now.[12,17] The contrived specimens were acceptable in Taiwan initially because of the low coronavirus cases. However, contrived clinical samples are inadequate to support the clinical performance of diagnostic tests. Natural clinical specimens are recommended by the United States and Taiwan. By contrast, there is no specific requirement for specimens or sample size in Singapore (Table 5).

The SARS-CoV-2 virus has mutated over time and rapidly, which is resulting in different variants in the COVID-19 pandemic. Thus, both Taiwan and the United States recommend manufacturers monitor new and emerging viral mutations and evaluate the impact on the test performance. It suggested that the impact of the mutations should not reduce the clinical performance of the test by 5% or more, at the same time, the clinical performance should demonstrate the PPA and NPA ≥95% or more.[17]

Most molecular tests are designed to detect a specific sequence, such as nucleocapsid (N) or spike (S) genes. Once mutations occur on a region of the genome targeted by the test, it can cause a false-negative result. The B.1.1.529 variant (also called Omicron) of SARS-CoV-2 virus was first reported in South Africa in 2021. The mutation of B.1.1.529 variant is in the S gene characterized by at least 30 amino acid substitutions and has more modifications than other SARS-CoV-2 variants. The United States designated Omicron as a Variant of Concern (VOC), and the US FDA has collaborated with the National Institutes of Health's (NIH) RADx program to analyze the impact of the variant on the performance of molecular tests.

Studies have demonstrated that some of the commercial tests failed to detect the SARS-CoV-2 omicron variant. These data suggested that the omicron variant may have reduced sensitivity.[19,20] For the above reasons, the emergency use approval provides a flexible regulatory pathway for COVID-19 tests in response to an urgent need.

7. THE IMPORTANCE AND PROSPECT OF DIAGNOSTIC TESTING FOR COVID-19

The epidemic caused by COVID-19 has aroused enormous attention from the public, society, and government. Global health experts have formulated detailed biosafety and protective measures, providing various detection methods and technologies for disease diagnosis in response to the pandemic. Nucleic acid detection has especially played an important role due to technical advantages, contributing feasible solutions to early diagnosis and disease monitoring. Although it offers accurate virus detection and is the important basis for confirming virus infection, a large number of suspected cases cannot be diagnosed by this technique. While antigen detections are not as accurate as nucleic acid detection, they serve as a good candidate for point-of-care testing (PoCT) and mass screening due to their operational simplicity and rapid readout accessibility.[21]

Table 5

Comparison of the requirements of clinical evaluation, stability and other studies for emergency use approval of SARS-CoV-2 nucleic acid tests between Taiwan, Singapore and the United States

	Clinical Evaluation	Reagent Stability	Specimen Storage and Shipping	Other Studies
Taiwan	(1) Natural clinical specimens. (2) 30 negative and 30 positive cases. (3) PPA and NPA ≥ 95%	Briefly describe stability test plan.	Conditional exemption	(1) Depend on the characteristics of the product.
Singapore	Exemption	Same as above.	Required	(1) Usability test (for PoCT).
The U.S.	(1) Natural clinical specimens. (2) 30 negative and 30 positive cases. (3) PPA and NPA ≥ 95% (4) Sample should include 25% of the low viral positive samples. (5) At least 20 positive samples and 100 negative sample are used for screening individuals without symptoms or other reasons.	Same as above.	Exemption	(1) Studies to support point-of-care indication. (2) Studies to support authorization of multi-analyte respiratory panels.

Conditional exemption: If the claim is the same as CDC requirements, the test can be exempted.

It is crucial for governments to implement an agile emergency regulatory framework that ensures a supply of quality test kits and essential medical products for their people as the medical industry is accelerating the development and production of test kits amid the pandemic. Meanwhile, continuous or additional evidence is required by the officials regarding postmarketing surveillance to safeguard the safety and quality of the products given emergency approval. However, the vast discrepancy of performance requirements between countries falls on the clinical evaluation such as whether to accept overseas clinical evaluation reports and using contrived specimens as well as the sample size required by the clinical research. The sample size and specimen types that are required for approval is generally adapted by the current situation of the countries due to the fluctuation of confirmed case numbers affected by the epidemic phase each country is in.

Health authorizations globally launch regulatory channels to accelerate the review and conditional approval and exemption of some performance requirements for essential medical products like the special manufacturing approvals issued in Taiwan and the EUA issued in the United States. In this review, we introduce the present emergency regulatory mechanism and the mandatory performance requirement for Special Manufacturing Approvals requisition in Taiwan. By comparing the emergency regulatory frameworks between Taiwan, Singapore, and the United States, this review provides references and insight to test developers on the research and development of IVD tests. Given the global COVID-19 epidemic situation and the rapidly changing characteristics of the virus, coordination between the public and government, and developing quick and quality diagnostic tests is imperative to managing the epidemic.

ACKNOWLEDGMENTS

This research was funded by the Food and Drug Administration, Ministry of Health and Welfare of Taiwan.

REFERENCES

1. Mohammadi M, Meskini M, do Nascimento Pinto AL. 2019 Novel coronavirus (COVID-19) overview. *Z Gesundh Wiss* 2022;**30**:167–75.
2. Yuan X, Yang C, He Q, Chen J, Yu D, Li J, et al. Current and perspective diagnostic techniques for COVID-19. *ACS Infect Dis* 2020;**6**:1998–2016.
3. Drexler JF, Gloza-Rausch F, Glende J, Corman VM, Muth D, Goettsche M, et al. Genomic characterization of severe acute respiratory syndrome-related coronavirus in European bats and classification of coronaviruses based on partial RNA-dependent RNA polymerase gene sequences. *J Virol* 2010;**84**:11336–49.
4. Chen Y, Liu Q, Guo D. Emerging coronaviruses: Genome structure, replication, and pathogenesis. *J Med Virol* 2020;**92**:418–23.
5. Taiwan Centers for Disease Control, Prevention and Control of COVID-19 in Taiwan, 2021-1-5. Available at: https://www.cdc.gov.tw/En/Category/Page/0vq8rsAob_9HCi5GQ5jH1Q. Accessed 5 January, 2021.
6. Paules CI, Marston HD, Fauci AS. Coronavirus infections-more than just the common cold. *JAMA* 2020;**323**:707–8.
7. Gulholm T, Basile K, Kok J, Chen SC, Rawlinson W. Laboratory diagnosis of severe acute respiratory syndrome coronavirus 2. *Pathology* 2020;**52**:745–53.
8. Yu L, Wu S, Hao X, Dong X, Mao L, Pelechano V, et al. Rapid detection of COVID-19 coronavirus using a reverse transcriptional loop-mediated isothermal amplification (RT-LAMP) diagnostic platform. *Clin Chem* 2020;**66**:975–7.
9. Österdahl MF, Lee KA, Lochlainn MN, Wilson S, Douthwaite S, Horsfall R, et al. Detecting SARS-CoV-2 at point of care: preliminary data comparing loop-mediated isothermal amplification (LAMP) to polymerase chain reaction (PCR). *BMC Infect Dis* 2020;**20**:783.
10. China National Medical Products Administration. Key Points of Technical Review for the Registration of 2019 Novel Coronavirus Nucleic Acid Detection Reagent. 2020-2-12. Available at: https://www.nmpa.gov.cn/directory/web/nmpa/zhuanti/yqyjzxd/yqyjxd/20200330170001581.html. Accessed 5 January, 2021.
11. Korea ministry of food and drug safety. Guidelines on the review and approval of in vitro diagnostic medical devices for COVID-19. November 2020. Available at: https://www.mfds.go.kr/eng/brd/m_40/view.do?seq=72625&srchFr=&srchTo=&srchWord=&srchTp=&itm_seq_1=0&itm_seq_2=0&multi_itm_seq=0&company_cd=&company_nm=&page=1. Accessed 5 January, 2021.
12. Taiwan food and drug administration. Special manufacturing approvals: Nucleic acid tests for SARS-CoV. 2021-11-16. Available at: https://www.fda.gov.tw/TC/siteListContent.aspx?sid=310&id=32908. Accessed 19 January, 2022.
13. Singapore Health Sciences Authority. HSA expedites approval of covid-19 diagnostic tests in singapore via provisional authorisation. Available at: https://www.hsa.gov.sg/docs/default-source/default-document-library/hsa-expedites-approval-of-covid-19-diagnostic-tests.pdf. Accessed 5 January, 2021.
14. Singapore Health Sciences Authority. Provisional authorisation of covid-19 diagnostic tests – key validation requirements. Available at: https://www.hsa.gov.sg/docs/default-source/hprg-mdb/provisional-authorisation-validation-requirements-for-covid-19-tests.pdf. Accessed 5 January, 2021.
15. COVID-19 Test Kits Authorised for Professional Use. Available at: https://www.hsa.gov.sg/announcements/regulatory-updates/covid-19-test-kits-authorised-for-professional-use. Accessed 9 April, 2022.
16. United States Food and Drug Administration. Policy for diagnostic tests for covid-2019 during the public health emergency. Available at: https://www.fda.gov/media/135659/download. Accessed 21 January, 2022.
17. United States Food and Drug Administration. Molecular diagnostic template. Available at: https://www.fda.gov/medical-devices/coronavirus-disease-2019-covid-19-emergency-use-authorizations-medical-devices/in-vitro-diagnostics-euas. Accessed 21 January, 2022.

18. United States Food and Drug Administration. Supplemental template for developers of molecular and antigen diagnostic covid-19 tests for screening with serial testing. 2021-10-25. Available at:https://www.fda.gov/medical-devices/coronavirus-disease-2019-covid-19-emergency-use-authorizations-medical-devices/vitro-diagnostics-euas. Accessed 21 January, 2022.
19. Science Brief: Omicron (B.1.1.529) Variant.2021-12-02. Available at: https://www.cdc.gov/coronavirus/2019-ncov/science/science-briefs/scientific-brief-omicron-variant.html. Accessed 09 April, 2022.
20. SARS-CoV-2 Viral Mutations: Impact on COVID-19 Tests. Available at: https://www.fda.gov/medical-devices/coronavirus-covid-19-and-medical-devices/sars-cov-2-viral-mutations-impact-covid-19-tests. Accessed 09 April, 2022.
21. Dinnes J, Deeks JJ, Adriano A, Berhane S, Davenport C, Dittrich S, et al; Cochrane COVID-19 Diagnostic Test Accuracy Group. Rapid, point-of-care antigen and molecular-based tests for diagnosis of SARS-CoV-2 infection. *Cochrane Database Syst Rev* 2020;8:CD013705.