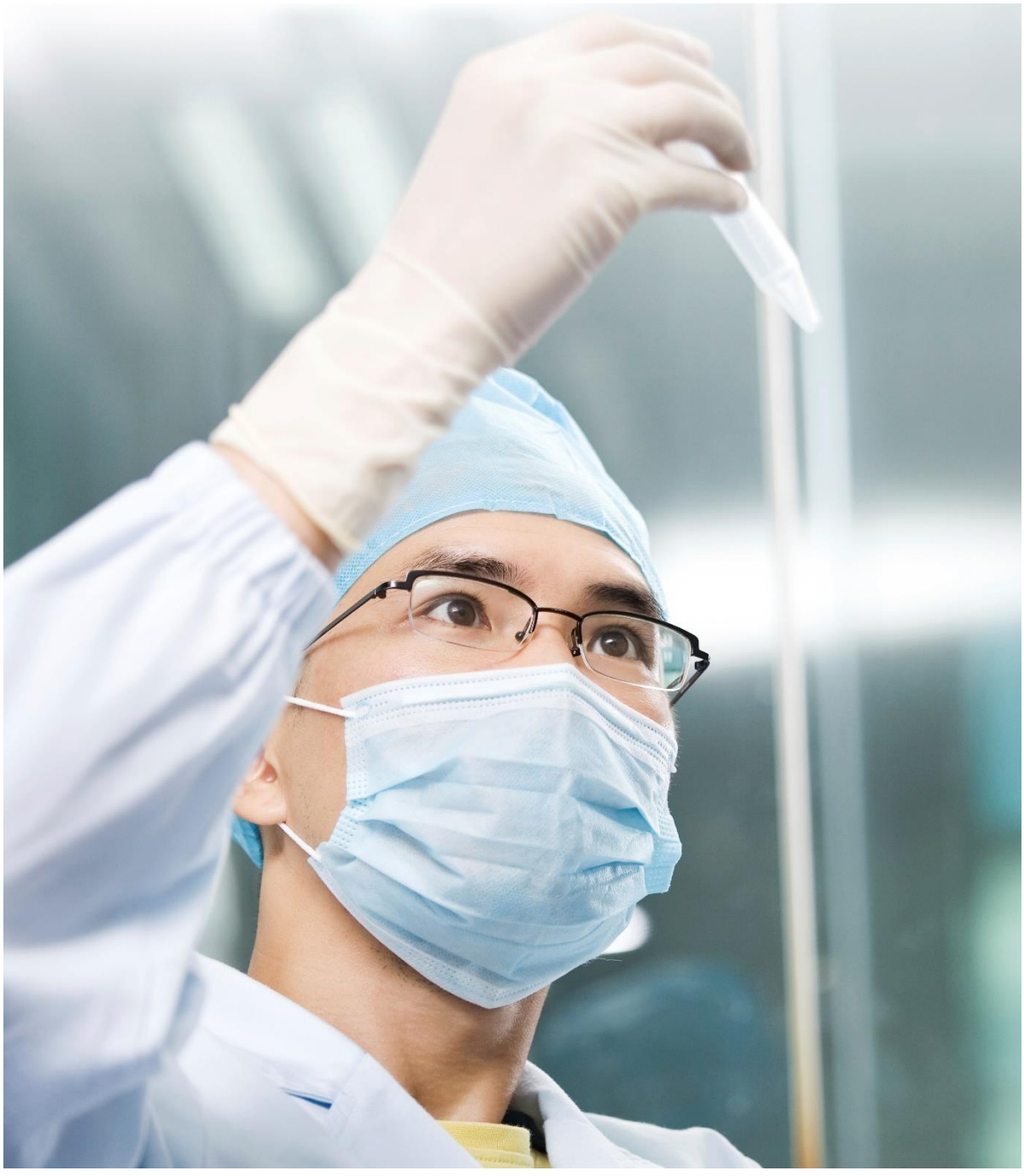

Building Regulatory Agility for Adequate Access to Quality SARS-CoV-2 Test Kits During the Global Pandemic

A Position Paper Prepared By

APACMed
The voice of MedTech

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Executive Summary

Since its discovery at the end of 2019, the novel coronavirus known as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) has claimed over 350,000 lives worldwide[1] and placed unprecedented strain on global healthcare systems, economies, and individual livelihoods. This has led to a rapidly increased demand for medical products and solutions to diagnose, treat, and manage the disease caused by this virus, also known as COVID-19. In a response to this urgent need, the healthcare industry has ramped up the production and R&D of essential medical products, with scientists and technicians working around the clock to develop innovative products and solutions.

In the absence of a vaccine, safe and reliable testing plays a critical role in the accurate tracking of cases, the timely conduct of contact tracing in the community, the isolation of infected individuals, and countries' preparation for potential new waves of infections as governments begin lifting lockdown measures.

There are various types of tests available on the market and they serve different purposes. Molecular tests aid in the diagnosis and confirmation of current infections. Serologic tests can play an important role in understanding the virus's epidemiology in the general population and identifying groups at higher risk for infection.

With the paramount demand to save humanity, governments are working under extreme pressures to bring these much-needed testing technologies into countries. Meanwhile, the speed and volume of innovations require the dedication of immense regulatory resources that no single country can or should manage alone. In this context, **it is apt timing for governments to examine whether their emergency regulatory mechanisms are truly agile, risk-calibrated, and fit-for-purpose, and consider what can be learnt from the regulatory experiences of other countries**.

The Asia Pacific Medical Technology Association (APACMed)[2] is the only regional trade association representing the medical technology industry in Asia Pacific. In this paper, regulatory professionals from the In Vitro Diagnostics (IVD) working group of the Association's Regulatory Affairs functional committee documented its observations of emergency regulatory mechanisms adopted in Asia Pacific, Europe, the United States, and the World Health Organization (WHO).

Three main categories of emergency regulatory mechanisms for adequate access to SARS-CoV-2 test kits were observed:

- To activate or create **emergency exemption/approval pathways** (sometimes named as **provisional or conditional approval**), which allows for fast access with limited preliminary clinical evidence and conditions attached to request for post-authorisation submission of ongoing or additional safety and performance evidence.
- To set up a separate **expedited pathway**, in parallel with or after the above-mentioned emergency pathways, in order to **prioritise regulatory resources** for review and approval of test kits, and to maintain this "fast track" for a longer time period to cater for the continuous innovation in response to the constantly evolving understanding of the SARS-CoV-2 virus.
- To leverage **regulatory reliance models** and/or **authorisations from overseas reference authorities** (such as IMDRF member countries or the WHO Emergency Use Listing procedure) to minimise duplication of efforts.

As we take a deep dive into the various categories of emergency regulatory mechanisms in our region, we have observed some gaps and areas for improvement in the fields of prioritising regulatory resources for COVID-19 related products for a sufficient period of time, leveraging knowledge from other countries, and harmonising requirements to enable better regulatory reliance and solidarity to jointly combat the pandemic.

Inspired by a recently published editorial in The BMJ[3], APACMed has proposed its **Key Recommendations** as outlined below:

- **To build regulatory agility during the pandemic.** Countries should remain agile and prioritise regulatory resources by creating and/or maintaining a "fast track" approval process for COVID-19 products until the global pandemic is over, with clear procedural and risk-calibrated technical requirements, to enable continuous innovation based on the evolving science of the virus.
- **To leverage regulatory reliance and convergence.** More countries should adopt regulatory reliance models and/or leverage reference agencies to reduce delays and minimise duplication of efforts; multi-lateral harmonisation platforms (such as WHO, IMDRF, AMDC, AHWP, and APEC-RHSC) should be further leveraged during the pandemic to share knowledge, promote reliance-based cooperation, and ensure synchronised and timely decisions on COVID-19 related products among regulatory authorities.
- **To ensure access to different types of test kits.** Countries should ensure adequate access to both molecular and serologic tests to ensure a robust testing strategy in the country, given that different tests serve different purposes and complement each other.
- **To build resilient global supply networks.** Countries should implement non-discriminatory emergency regulatory mechanisms that enable adequate and timely access to high quality COVID-19 products from countries across the world, to improve the resilience of the supply networks.
- **To adopt acceptance of overseas performance evaluation.** In order to reduce delays and burdens for official laboratories, countries should follow international best practices in accepting overseas performance evaluation, rather than duplicating the efforts via local type testing.
- **To allow for contrived clinical specimens.** A reasonable portion of contrived specimens should be acceptable, given that it is unlikely clinical specimens will always be available in the volumes required, especially since countries are experiencing fluctuating numbers of cases.
- **To follow the proposed phased approach**. Countries should follow our proposed phased approach as described in Section IV of this paper and opt for the most appropriate combination of regulatory mechanisms and tools, as they navigate through different phases of the pandemic.

Notes:

1. Data retrieved end of May from the WHO Coronavirus Disease (COVID-19) Dashboard
2. The Asia Pacific Medical Technology Association (APACMed) represents the suppliers and manufacturers of medical equipment, devices and in-vitro diagnostics, industry associations and other key stakeholders associated with the medical technology industry in Asia Pacific.
3. Mak, T. K., Lim, J. C., Thanaphollert, P., Mahlangu, G. N., Cooke, E., & Lumpkin, M. M. (2020). Global regulatory agility during covid-19 and other health emergencies. *Bmj*, m1575. doi: 10.1136/bmj.m1575 (https://www.bmj.com/content/bmj/369/bmj.m1575.full.pdf).

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Abbreviations

AHWP	Asia Harmonization Working Party
AMDC	ASEAN Medical Device Committee
APEC RHSC	Asia Pacific Economic Cooperation Regulatory Harmonization Steering Committee
CDC	Centers for Disease Control and Prevention
COVID-19	Coronavirus Disease 19
EUA	Emergency Use Authorization
EUL	Emergency Use Listing
FIND	Foundation for Innovative New Diagnostics
GHTF	Global Harmonization Task Force (it was replaced by IMDRF in 2011)
IMDRF	International Medical Device Regulators Forum
IVD	In Vitro Diagnostics
LDT	Laboratory Developed Test
MDSAP	Medical Device Single Audit Program
NIID	National Institute of Infectious Diseases (Japan)
NTL	National Testing Laboratories (Malaysia)
PCR	Polymerase Chain Reaction
PMS	Post Market Surveillance
QMS	Quality Management System
RUO	Research Use Only
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
TTT	Tests, Tracks people infected and Traces their contacts
WHO	World Health Organization

I. Introduction

Since the end of 2019, the world has been in the grip of the novel coronavirus, SARS-CoV-2, which has recorded over six million confirmed cases and more than 350,000 deaths by end of May 2020. Declared by the WHO as a global pandemic on 11th March 2020, COVID-19 has placed unprecedented strain on global healthcare systems, economies, and individual livelihoods.

As an association, the Asia Pacific Medical Technology Association (APACMed) recognises the vital role of the MedTech industry in the provision of critical support in response to COVID-19, from diagnosis to treatment, around the world. Jointly with its members, APACMed works with governments and peer associations on the ground, to ensure supply of essential medical products in the Asia Pacific region and beyond.

APACMed commends the efforts of many governments in the Asia Pacific region for its commitment to preventing and slowing the further spread of COVID-19 via numerous approaches, including the use of a robust testing strategy. In a race to bring much-needed equipment and testing technologies into their countries, health authorities are working around the clock to implement a **risk-calibrated decision-making process** to meet this paramount demand.

As the MedTech industry is ramping up R&D and production of testing products and solutions, the sheer speed and volume of innovations require a dedication of regulatory resources too immense for any single country to manage alone. In this context, it is apt timing for governments to examine if its emergency regulatory mechanism is truly agile and fit-for-purpose, and consider how to cultivate and leverage reliance models as well as learn from regulatory experiences in other countries.

Regulatory professionals from the In Vitro Diagnostics (IVD) Working Group within APACMed's Regulatory Affairs functional committee have documented in this paper a variety of regulatory efforts made by health authorities in the Asia Pacific region, as well as in the United States, European Union, and WHO, in granting adequate access to COVID-19 test kits.

The purpose of this paper is to share knowledge and best practices, as well as shed light on the rationale and key elements for building an agile and fit-for-purpose emergency regulatory framework that caters to continuous innovation and, most importantly, the needs of national testing strategies throughout multiple phases of the pandemic.

The healthcare community's knowledge and understanding of this virus is in a state of constant evolution, and clinicians and scientists around the world are working tirelessly to validate, adapt, and re-validate treatment protocols and medical products for COVID-19. Health authorities globally are also updating their policy regimes to account for the growing amount of scientific and clinical evidence they receive.

This paper was based on publicly available information, current of the published date, as well as observations made by regulatory professionals in the medical device industry. APACMed recognises that the global landscape is changing rapidly and welcomes policy makers, regulators, industry peers, researchers, and other experts to share their comments and feedback with us for the purpose of further refinement of this paper.

II. Importance of Adequate Access to Quality SARS-CoV-2 Tests

During a WHO media briefing, Director-General Dr Tedros Adhanom Ghebreyesus said: "We have a simple message for all countries: test, test, test."

While diagnostics remain the bedrock for healthcare, its role, now more than ever, is critical in managing and containing an outbreak. In the absence of a vaccine, safe and reliable testing plays a critical role, in accurately tracking cases, timely contact tracing, proper isolation of infected individuals, and in preparation for potential waves of infections as governments begin lifting lockdown measures.

In the response to COVID-19, testing is used for the following key purposes:

- First, for **diagnosis** and **active case finding**: To identity infected individuals early and isolate them with appropriate care; and to conduct timely contact tracing around confirmed cases to prevent further transmissions.
- Second, for **surveillance** purposes: To monitor different groups of people with higher risk of contracting or transmitting the disease (such as Healthcare Professionals, essential service workers, vulnerable people, travelers, etc.).
- Third, for **epidemiological and clinical studies**: To learn more about the new virus, the infection rate of the community, the groups at higher risks of infection, as well as to assist in validating efficacies of new medical products (cure, vaccines, etc.).

In general, there are two types of tests: **molecular and serological**. Molecular tests have been mostly used to diagnose and/or confirm cases for clinical treatment or surveillance purposes. However, there are characteristic limitations to molecular tests when responding to a long-term outbreak, since these tests only detect the presence of virus, but cannot provide a diagnostic result for someone who was infected previously and has already cleared the infection. According to the *US CDC*, **although serologic tests should not be used at this time to determine if an individual is immune, these tests can help determine the proportion of a population previously infected with SARS-CoV-2 and provide information about populations that may be immune and potentially protected**.

As highlighted in the *OECD Policy Responses to COVID-19*, given the characteristics of this coronavirus – including the large number of asymptomatic (and pre-symptomatic) cases and high reproduction number – to be effective at suppressing the spread of the virus, the Tests, Tracks people infected and Traces their contacts (TTT) strategy should be used widely, requiring a large proportion of all cases (between 70 and 90%) to be traced to prevent a new outbreak. The report also mentioned that the successful implementation of serologic testing strategy at large scales can complement the TTT strategy.

In summary, reliable molecular and serologic tests play a critical role for any country to roll out a successful testing strategy throughout different phases of this pandemic. While the industry is ramping up the R&D and production of test kits at full speed, governments across the globe are still in need of quality test kits among other essential medical products for their own populace. It is therefore **crucial to create an agile and fit-for-purpose emergency regulatory framework that is risk-calibrated according to public health hazards caused by COVID-19 and the potential benefits a reliant test can bring to control the pandemic.**

III. Emergency Regulatory Mechanism for SARS-CoV-2 Test Kits

In his blog post "The first modern pandemic", Bill Gates said:
"It is like a world war, except in this case, we're all on the same side."

Multi-stakeholder collaboration across the industry and national borders is needed to enable global innovation that minimises the damage to lives and economies. When it comes to innovation, it is not only product innovation for testing, treatments, vaccines, but also **innovation in policies and regulations that enable those product innovations to reach patients**.

The sheer volume and speed of innovation can place substantial strain on countries' available regulatory resources. As reported in the WHO *International Clinical Trials Registry Platform (ICTRP)*, as of 25 May 2020, there were a total of 2,845 entries of clinical trials related to COVID-19 medical products. With regards to test kits, there are more than 670 SARS-CoV-2 tests commercially available or in development according to the *FIND database*.

During this unprecedented public health emergency, both government and public are seen to have a different tolerance level for risks compared to normal times, leading to **a calibrated benefit-risk assessment being adopted by many regulators, weighed against the heightened risk brought by this pandemic of the century.**

APACMed commends health authorities in the region for setting up emergency regulatory mechanisms to provide timely access to essential medical products, but also for their adaptation of these mechanisms to cater for the complex and rapidly evolving science and innovations around COVID-19. This has allowed product authorisations being granted within weeks or even days through the emergency pathways, which is a significant achievement during the global pandemic.

In this section, we will discuss three aspects of emergency regulatory mechanisms for SARS-CoV-2 Test Kits based on our observations from key markets in Asia Pacific, in comparison with Europe, US and the WHO, including: i) main categories of emergency pathways; ii) overview of the approved test kits, and iii) key regulatory considerations in emergency approvals.

i. Main Categories of Emergency Pathways

We have documented a variety of Emergency Regulatory Pathways from the Asia Pacific region, Europe Union, US and WHO, which we then categorized into the three groups below.

- To activate or create **emergency exemption/approval pathways** (sometimes called **provisional/conditional approval**), to allow fast access with limited preliminary clinical evidence and conditions attached to request for post-authorisation submission of ongoing or additional safety and performance evidence.
- To set up a separate **expedited pathway**, in parallel with or after the above-mentioned emergency pathways, in order to **prioritise** regulatory resources for review and approval of test kits, and to maintain this "fast track" for a longer time period to cater for the continuous innovation in response to evolving understanding of SARS-CoV-2.

- To leverage **regulatory reliance models** and/or **authorisations from overseas reference authorities** (such as IMDRF member countries or the WHO Emergency Use Listing procedure), to minimise duplication of efforts.

As indicated in **Table 1** below, we see that most countries allow the emergency regulatory pathways (in **Column A**) to persist for a reasonable time period (usually a few months) or until the pandemic is over. Following (or in parallel with) these emergency pathways, many countries have also put in place a separate Prioritised or Expedited pathway (in **Column B**) to meet the demands emerging from this longstanding pandemic. This measure is crucial because much remains unknown about this virus; both physicians and scientists are updating the care and products in response to evolving science emerging about the virus. We recommend that **countries remain agile and prioritize their regulatory resources by creating or maintaining a fast track approval process for COVID-19 products until the global pandemic is over, with clear procedural and risk-calibrated technical requirements, to enable continuous innovation based on the evolving science of the new virus.**

To quote a recent editorial published in The BMJ: "Countries lacking emergency regulatory processes can rely on the WHO emergency use listing (EUL) mechanism or the work of other trusted agencies, to inform their regulatory decisions and reduce delays and duplication of effort, provided they receive the same version of the product reviewed by the reference authority or WHO."

As illustrated in **Column C**, several countries in this region have leveraged either regulatory reliance models or reference authorities in other countries. However, as the unprecedented speed of COVID-19 innovation is draining regulatory resources worldwide, we believe that more needs to be done in this field. We recommend that **more countries adopt regulatory reliance models or leverage reference agencies to reduce delays and minimise duplication; meanwhile, multi-lateral harmonisation platforms (such as WHO, IMDRF, AMDC, AHWP, and APEC-RHSC) should be further leveraged during COVID-19 to share knowledge, promote reliance-based cooperation, and ensure synchronised and timely decisions on COVID-19 products among regulatory authorities**.

Table 1: Emergency regulatory pathways for SARS-CoV-2 Test Kits in Asia Pacific, EU, US and WHO

	(A) Emergency Exemption or Approval (sometimes named as Provisional or Conditional Approval)	(B) A separate Prioritised or Expedited pathway in parallel with or post the Emergency pathway listed in column (A)	(C) Leverage the Reliance model or authorisation from overseas reference agencies	Timeline*
Australia	Emergency exemption for import (to accredited laboratories; open for 9-10 months)	Expedited assessment (full submission, ongoing evidence to be provided within 12 months of approval)	MDSAP QMS	1-2 weeks for expedited approval
China	Emergency approval (high threshold since Feb when the review guideline was published; complete clinical data to be submitted for renewal registration within 1-year)			13 working days after entering emergency pathway (according to the MD Emergency Approval Notification published in 2009)
Japan	Conditional Approval (missing study data to be submitted by the defined due date to obtain full approval)	Prioritised review (full review)		1-2 weeks for the conditional approval
Korea	1st EUA approval (provisional approval, and open for application for 1 month, till end of Feb) 2nd EUA for rapid PCR test (open for 1-5 June)	Expedited review (full submission) (open for 2 months till end of June)		2-8 weeks for the 1st EUA approval
India	Emergency provisional approval (conditions stated on the license to be fulfilled; full local evaluation post pandemic)	Prioritised Review	US FDA EUA and CE IVD certifications for imports	7 days
Singapore	Provisional authorisation (Periodic reports on specific data to be submitted to HSA post authorisation to assure the continued performance)			1-3 weeks
Vietnam	Prioritised approval (it is expected to end by June 2020)			2-4 weeks
Philippines	Special Certification		US, EU, Japan, Australia, Canada (previously known as GHTF member countries), Korea, Singapore, WHO EUL, and others	1-2 weeks
Thailand	Special exemption of import for Government hospitals	A new special guidance on testing of SARS-CoV-2 test kits via a normal route	EU	4-8 weeks
Indonesia	Emergency exemption for import (open for 3 months till end of June; letter issued by BNPB)	In parallel with BNPB letter, COVID-19 products (approved and freely sold in sourcing country) go through MoH expedited registration with full submission requirements (serologicand rapid test registration are not accepted)		2-3 weeks for MoH approval of import products
Malaysia	Emergency Special Access		US, EU, Canada, Japan, Australia, WHO EUL	4-6 weeks
US	EUA (Open till emergency status is terminated)			15 business days
EU				Self-declaration of conformity
WHO	Emergency use listing (EUL)			2-3 weeks

** Data in the last column of **Table 1** for "Timeline" was based on either regulatory documents or our members' observations where official information was not available. Thus, the data cannot be understood as factual for all submissions nor as prediction for future approval timelines.*

ii. Overview of Approved SARS-CoV-2 Test Kits

An overview of approved SARS-CoV-2 test kits in Asia Pacific, Europe, US and the WHO is shown in **Table 2**, based on publicly available information from the websites of regulatory authorities and the WHO's collated table (hyperlinks embedded in the first column will direct the reader to the **country-specific list of approved test kits**).

Many key markets in Asia Pacific region and beyond have granted access to a variety of test kits in terms of technologies employed and countries they are sourced from, acknowledging the fact that different types of test kits are playing differentiated roles in ensuring a successful testing strategy to respond to the pandemic.

However, we also see that some countries have not granted access to any serologic tests, which complements molecular tests in providing intelligence on the severity of the disease, groups with higher risks of infection, or populations that may be immune and potentially protected. Since most countries are re-opening in a gradual and cautious manner, we recommend that **countries should ensure adequate access both to molecular and serologic tests to ensure a robust testing strategy in the country, given that different tests serve different and complementary purposes.**

Table 2: Overview of SARS-CoV-2 test kits approved in Asia Pacific, EU, US and WHO *(excluding domestically manufactured export-only products)*

	Number of Molecular tests	Number of Serologic tests	Total Number	Country of legal manufacturers
Australia (as of 7 May)	17	31	48	Local, China, Korea, Denmark, UK, Spain, US
China (as of 30 April)	19	11	30	***Local only***
Japan (as of 21 May)	6	1	7	Local, China, US
Korea (as of 11 MAY)	6	0	6	***Local only***
India (as of 6 May)	66	95	161	Local, China, Korea, Canada, Germany, Israel, US, UK, Spain, France, etc.
Singapore (as of 7 May)	27	10	37	Indigenous, China, Korea, US, etc.
Vietnam	7	2	9	Local, Korea, Germany, China, etc. Updated Roche
Philippines (as of 14 May)	39	44	83	Local, China, Korea, Singapore, France, Spain, UK, US, etc.
Thailand (as of end of April)	14	3	17	China, US, Singapore, Germany, Spain, Korea, Malaysia, etc.
Indonesia (as of May)	7	0	7	Local, Korea, US, Singapore, Spain, China (only molecular tests accepted by MoH)
Malaysia (official data not available)	6	0	6	Local, China, Korea, EU, US, etc.
US (as of end of April)	38	4	42	Local, UK, Korea, Germany, China, Canada
EU (as of 6 April)	78	101	179	Local, China, Korea, US, etc.
WHO EUL (as of 27 April)	4	0	4	US, UK, China, etc.

We also observed that some markets in our region have only granted authorisations to domestic products. Considering the globally synchronised and collaborative efforts in developing, manufacturing, and distributing the essential and innovative medical products for all (as demonstrated by the Global Initiative COVID-19 Technology Access Pool), we recommend that **countries should implement non-discriminatory emergency regulatory mechanisms that enable adequate and timely access to high quality COVID-19 products from countries across the world, to further improve the resilience of its supply networks.**

iii. Key Regulatory Considerations for Emergency Approvals

To compare regulatory considerations for emergency approvals of SARS-CoV-2 test kits, we have looked into guidance documents issued by regulatory authorities in Asia Pacific, EU, US and WHO, mainly focusing on three areas: the quality management system (QMS), post-market surveillance (PMS), and clinical evidence.

Since many emergency regulatory decisions are made based on limited preliminary scientific evidence to address the urgent needs posed by the public health crisis, regulatory authorities would very much focus on assessing the **robustness of the quality management system**. Some countries and the WHO refer to the international standard ISO 13485: 2016 while others refer to local GMP standards.

Similarly, regulatory authorities are paying more attention to the post-authorisation surveillance, with a request for submission of **ongoing or additional evidence** to ensure the safety and performances of the products that were approved through the emergency pathways. Some countries request all such products to follow post-market surveillance protocols specific to emergency approvals while others only request certain types of products to follow a more stringent post market surveillance protocol.

The greatest deviations we observed were in the requirements for clinical evidence, for which we have chosen three elements to illustrate in **Table 3**, including acceptance of contrived clinical specimen, required sample size of clinical studies, and acceptance of overseas clinical performance evaluation.

Table 3: *Key deviations in regulatory considerations in clinical evidence for emergency approval of SARS-CoV-2 test kits*

	Acceptance of contrived clinical specimen	Required sample size of clinical studies	Acceptance of overseas clinical performance evaluation
Australia	✓	A scientifically valid sample size	✓ (if the evaluation is done by recognised MDSAP or ISO certificate manufacturer)
China	✗	A minimal of 200 natural positive specimens and 300 natural negative specimens	✓ (if it meets the China IVD GCP according to the general guidance issued in 2018. But clinical trials need to be conducted in 3 clinical institutes; type testing to be conducted in qualified testing institutes using local national reference material)

Japan	✓ (allow for a portion)	150	✓ (but additional comparison data with the NIID method is required)
Korea	1st EUA: Not applicable 2nd EUA for rapid PCR: No contrived sample allowed Expedited review: ✓ (under 30% is acceptable)	1st EUA: Not applicable 2nd EUA for rapid PCR: 30 positive and 30 negative Expedited review: sample size shall be justifiable and valid to claim clinical effectiveness (sample calculation formula attached in the guideline)	1st EUA: Not applicable. 2nd EUA for rapid PCR: Korean samples recommended Expedited review: Yes if it meets Korea IVD clinical performance study requirements & COVID-19 IVD registration guideline (the guideline suggests the use of Korea EUA assays as reference standard)
India	Not indicated (however, the sites decide based on the IFU of the product)	Sample size is decided as per the objective of the study and claims as per IFU.	✓ (overseas clinical performance evidence from UK, USA, Australia, Canada & Japan is accepted)
Singapore	✓	Serology tests: at least 50 positive and negative clinical samples according to the Key evaluation requirements	✓
Vietnam	Not defined	Not defined	✓ (but local testing is required for non-legalized FSC)
Philippines	For Molecular: N/A For Serological: ✗	For Molecular: N/A For Serological: 300 tests	For Molecular: N/A For Serological: ✗
Thailand	Not indicated	Serological: 200 tests Molecular: 100 tests	✗ (Overseas reports are only accepted if the national labs are not able to perform the local evaluation)
Indonesia	Not indicated	Not indicated	✓
Malaysia	Not indicated	Minimum of 100 tests	Partial (accepted but still require local validation report by NTL)
US	✓ (in the absence of known positive samples for testing)	a minimum of 30 contrived reactive specimens and 30 non-reactive specimens	✓
EU	Not indicated (depends on risk assessment)	Not indicated (depends on risk assessment)	✓

WHO	✓ (25 natural clinical specimens are required but the rest can be contrived)	A minimum of 50 clinical positive and 100 negative specimens	✓

As illustrated in **Table 3**, it is acceptable in many markets to use contrived specimens. **As countries are experiencing different stages of the pandemic with fluctuating numbers of cases, it is unlikely that clinical specimens will always be available in the volumes required for all analytical studies, therefore we recommend that a certain portion of contrived specimens should be acceptable.**

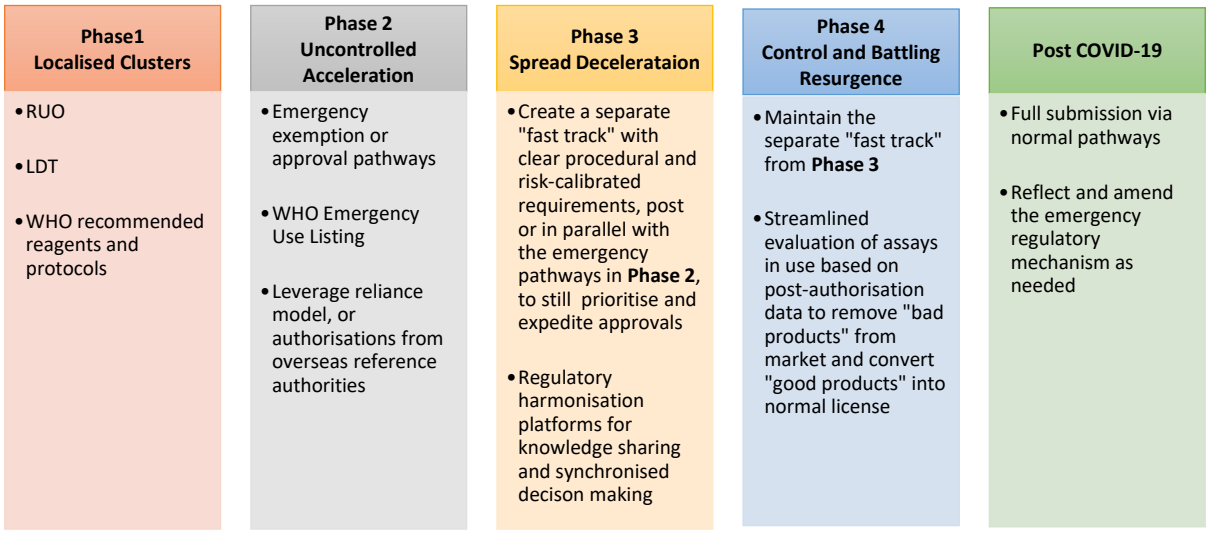
Besides, the required sample sizes for clinical studies also vary greatly across different markets. However, given it is to assess the clinical performance of diagnostic technologies for the same pathogen, this variation is unlikely to be scientifically justifiable and it might be just one example out of the many variations in clinical evaluation across markets. Therefore, to ensure equitable access for patients and optimal efficiency in global regulatory decision makings, especially during the pandemic, we would highly recommend health authorities to better harmonise requirements and practices in clinical evaluation.

We also observe that some markets in Asia Pacific do not accept overseas clinical performance evidence, whilst other countries do accept it to differing extents. Please refer to a separate *APACMed position paper* for more information on the rationale and benefits brought by acceptance of overseas clinical performance evaluation. **In order to reduce delays and burdens for official laboratories, we recommend that countries should follow international best practices and accept overseas performance evaluation, rather than duplicating the efforts via local type testing.**

IV. Recommendations on a Phased Approach for Building Regulatory Agility During Pandemic

As the new coronavirus continues to spread rapidly around the world, we have seen countries experiencing different phases of a pandemic. Despite variations in paces, we see commonalities in the need to **adapt policy and regulatory mechanisms to cater for the different needs throughout multiple phases**. With reference to the four disease progression phases model developed by *McKinsey & Co.*, we have illustrated in **Figure 1** the APACMed recommendation on a phased approach to build regulatory agility via opting for suitable regulatory mechanisms or tools in each of the four phases during a long-standing global pandemic.

Figure 1: APACMed recommendation on a phased approach to build regulatory agility during COVID-19 pandemic for adequate access to SARS-CoV-2 test kits



During **Phase 1**, the onset of the pandemic, countries often rely on research use only products (RUOs) and laboratory-developed tests (LDTs), which are sometimes exempted from emergency approvals by regulatory authorities. It is also recommended to leverage the reagents and protocols provided by the WHO in this phase. These measures were deemed as effective in the early phase when the need to test for infections was paramount, with no other products available in the market.

The *WHO* encourages countries with no testing capacity and national COVID-19 laboratories with limited experience in COVID-19 virus testing to send the first five positive and the first 10 negative COVID-19 samples to WHO-identified reference laboratories for confirmatory testing of COVID-19. Quality tests for diagnosis or for confirmatory testing allow public health officials to determine who is infected and therefore requires isolation from others, and which of their contacts likewise require isolation. Such information allows for more precise targeting of public health responses, making it possible to avoid quarantining the entire population and shutting down large swaths of the economy.

During **Phase 2**, some products would have been developed with reasonably sufficient performance data from the laboratories; however, given the emergency situation, it is not feasible to wait for the complete set of data same as the normal times. Thus, it is critical for regulators to make fast and risk-calibrated decisions through their own emergency exemption/approval (sometimes named as

Provisional or Conditional Approval) pathways, or to leverage the WHO Emergency Use Listing (EUL), as well as product authorisations made by reference authorities in other countries. Safety and performance of products approved via emergency approvals will be further evaluated based on additional or on-going evidence collected post authorisation.

During **Phase 3**, after countries pass the peak of the first wave, it is essential to create a separate "fast track", post or in parallel with the emergency pathways in **Phase 2**, with clear procedural and risk-calibrated requirements, to ensure that regulatory resources are still prioritised for SARS-CoV-2 test kits review and approval. This measure is crucial, given much remains unknown about this virus and both physicians and scientists are updating the care and products in response to evolving science emerging about the virus. We recommend that regulators also maximise the benefits of regulatory harmonisation platforms (such as WHO, IMDRF, AMDC, AHWP, APEC RHSC, etc.) to share knowledge and leverage each other's best practices for a synchronized and efficient decision-making process.

During **Phase 4**, we recommend maintaining the separate "fast track" from phase 3, as we are combating with a long-standing global pandemic with possibly additional waves of infections. Again, we need to keep the "green channel" open, to prioritise and expedite COVID-19 product approvals until the pandemic is over globally. Regulators are also recommended to collaborate with other regulatory agencies or third-parties in conducting streamlined evaluation of assays in use based on post-authorisation data, with the aim of removing "bad products" from market and converting "good products" into normal license in an efficient manner. During this phase, it is also critical to have quality tests to detect asymptomatic (and pre-symptomatic) cases and help assess the efficacy of the cure and vaccines, as well as set up long-term surveillance infrastructure for vulnerable groups or those in high-risk settings.

It is important to note that those regulatory regimes or tools listed in each of the four phases are not mutually exclusive. Therefore, as countries move from one phase to the next, they can maintain the regulatory tools from previous phases and opt for the suitable combination of tools, based on the local resources and needs.

Lastly, as we march into the era of **Post COVID-19**, we expect regulatory submissions to be back to normal tracks. However, we do foresee that governments might reflect on this journey and upgrade the national emergency response plan including emergency regulatory mechanisms, to better harmonize with peers in other countries, and better prepare themselves for the next pandemic.

V. Conclusion

As more countries are re-opening the economies, increased testing rates will lead to an increased demand for available test kits and may lead to global shortages, despite manufacturers and testing facilities ramping up their capacities. As estimated previously by *McKinsey & Co.*, the global availability of PCR test kits (extraction and amplifications steps) is around 20 million kits per week, and is insufficient to meet global demand, if the US' requirement of 4.5 million tests per week is to be used as an indication.

Much remains unknown about SARS-CoV-2, even as we march into the volatile and long-standing Phase 3 or Phase 4 of the outbreak. Hence, it is apt timing for governments to assess the agility and appropriateness of their regulatory mechanisms as part of their national emergency response plan, benchmarked against key markets in the region and globally. We hope our observations and recommendations from this paper can assist governments in adjusting emergency regulatory mechanisms to ensure adequate access to high quality test kits, which are essential for implementing a successful testing strategy in the coming months.

As an Association, we believe that it is only through multi-stakeholder collaborations and solidarity in unity can countries, governments, health authorities and the general public across the world fully leverage the power of innovation to help us get through this pandemic together. This paper was based on the current publicly available information at the time of publishing as well as observations made by regulatory professionals in the medical device industry. We recognise that the global landscape is changing rapidly and welcome policy makers, regulators, industry peers, researchers, and other experts to share their comments and feedback with us for the purpose of further refinement of this paper.

On a final note, testing alone cannot substitute for other important preventative measures like social distancing, physical barriers, and infection control. Individual responsibility in upholding good personal hygiene, minimising physical contact with others, and seeking medical help when feeling unwell are all also critical aspects of the overall strategy. Together, we can slow down transmissions, beat the virus, and emerge stronger after the crisis.

VI. References

Australia	Therapeutic Goods (Medical Devices—Accredited Pathology Laboratories) (COVID-19 Emergency) Exemption 2020 https://www.legislation.gov.au/Details/F2020N00032 Post market review of COVID-19 point-of-care tests https://www.tga.gov.au/post-market-review-covid-19-point-care-tests Use of point of care testing https://www.tga.gov.au/covid-19-point-care-tests COVID-19 test kits included in the ARTG for legal supply in Australia https://www.tga.gov.au/covid-19-test-kits-included-artg-legal-supply-australia
China	Procedures for Emergency Approval of Medical Devices http://www.nmpa.gov.cn/WS04/CL2197/324626.html Key Points of Technical Review for the Registration of 2019 Novel Coronavirus Nucleic Acid Detection Reagent https://www.cmde.org.cn/CL0004/20447.html Key Points of Technical Review for the Registration of 2019 Novel Coronavirus Antigen/Antibody Detection Reagent https://www.cmde.org.cn/CL0004/20512.html Guidelines for accepting technical data for overseas clinical trials of medical devices https://www.cmde.org.cn/CL0112/6938.html Summary of NMPA approved novel coronavirus 2019-nCoV test kits http://english.nmpa.gov.cn/2020-04/03/c_468570.htm
India	Notice X-11026/07/2020-PRO for expedited review and approval of In Vitro Diagnostic Kits for diagnosis of COVID-19 https://cdsco.gov.in/opencms/opencms/system/modules/CDSCO.WEB/elements/download_file_division.jsp?num_id=NTc3MA== PCR, Rapid / CLIA / ELISA Kits approved for testing of Covid-19 https://cdsco.gov.in/opencms/opencms/en/Latest-Public-Notices/
Indonesia	Kepmenkes HK.01.07/MENKES/218/2020: Licensing Exemption for Importation and Distribution of Certain Medical Devices http://farmalkes.kemkes.go.id/en/?wpdmact=process&did=NzEwLmhvdGxpbms= Update on COVID-19 to allow importation for some essential products https://peraturan.bpk.go.id/Home/Details/134757/keppres-no-9-tahun-2020 SARS-CoV-2 test kits approved in Indonesia http://infoalkes.kemkes.go.id/

Japan	List of Authorized In Vitro Diagnostics (IVDs) for COVID-19 https://www.mhlw.go.jp/stf/newpage_11332.html
Korea	Guidelines on application for approval and review of COVID-19 In Vitro Diagnostics Medical Device List of COVID-19 Diagnostic Kits Authorized for Use under Emergency Use Authorizations https://www.mfds.go.kr/eng/brd/m_52/view.do?seq=74424&srchFr=&srchTo=&srchWord=&srchTp=&itm_seq_1=0&itm_seq_2=0&multi_itm_seq=0&company_cd=&company_nm=&page=1
Malaysia	Guidance Document: Import and/or Supply of Special Access Medical Device https://portal.mda.gov.my/industry/exemption/special-access-medical-device.html
Philippines	Issuance of Special Certification for Imported Test Kits of COVID-19 https://www.fda.gov.ph/fda-memorandum-no-2020-006-issuance-of-special-certification-for-imported-test-kits-of-covid-19/ Performance Testing of Antibody Test kits with Issued Special Certification https://www.fda.gov.ph/wp-content/uploads/2020/04/FDA-Memorandum-No.-2020-011.pdf List of COVID-19 Registered Kits https://drive.google.com/drive/folders/1Dk8KjbCzk8g92HydWDRvg8K-ATp7gBez?fbclid=IwAR2v60QZvEV-cV18ft2ZLtvighX6oxCtn3_pWv41fUY2fxjdRo3joNxpXV0
Singapore	HSA Expedites Approval of COVID-19 Diagnostic Tests in Singapore via Provisional Authorisation https://www.hsa.gov.sg/announcements/regulatory-updates/hsa-expedites-approval-of-covid-19-diagnostic-tests-in-singapore-via-provisional-authorisation Key Evaluation Requirements https://www.hsa.gov.sg/docs/default-source/hprg-mdb/provisional-authorisation-validation-requirements-for-covid-19-tests.pdf
Thailand	Ordinance: Required documents for obtaining registration certificate of imported COVID-19 Test Kits and Reagents Announcing the submission of assessment requests and the issuance of assessment certificates for test kits and reagents related to the diagnosis of SARS-CoV-2 infections (COVID-19 pathogens) Specifications for the request form, the list of supporting documents and the assessment certificate for diagnostic kits and drugs related to the diagnosis of SARS-CoV-2 infections (COVID-19 pathogens) Production and import manual for SARS-CoV-2 test kits and reagents

Vietnam	Letter Re: Manufacturing/importation of medical devices /in vitro diagnostics to diagnose SARS-CoV-2 virus
US	Emergency Use Authorization https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization#2019-ncov Policy for Diagnostic Tests for COVID-2019 during the Public Health Emergency https://www.fda.gov/media/135659/download
EU	Directive 98/79/EC of the European Parliament and of the Council of 27 October 1998 on in vitro diagnostic medical devices https://eur-lex.europa.eu/legal-content/EN/ALL/?uri=CELEX:31998L0079 Guidelines on COVID-19 *in vitro* diagnostic tests and their performance https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:52020XC0415(04) Current performance of COVID-19 test methods and devices and proposed performance criteria - Working document of Commission services https://ec.europa.eu/docsroom/documents/40805 Communication from the Commission Guidelines on COVID-19 in vitro diagnostic tests and their performance 2020/C 122 I/01 https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:52020XC0415(04)#ntr7-CI2020122EN.01000101-E0007
WHO	COVID-19) technical guidance: Laboratory testing for 2019-nCoV in humans https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance/laboratory-guidance Invitation to manufacturers of in vitro diagnostics for SARS-CoV-2 to submit an application for emergency use listing by WHO (date issued 28 February 2020) https://www.who.int/diagnostics_laboratory/200304_invitation_to_manufacturers_of_an_vitro_diagnostic_for_ncov.pdf?ua=1 Emergency Use Listing of IVDs-- Instructions for Submission Requirements: In vitro diagnostics (IVDs) Detecting SARS-CoV-2 Nucleic Acid (23 March 2020) https://www.who.int/diagnostics_laboratory/200324_final_pqt_ivd_347_instruction_ncov_nat_eul.pdf?ua=1 COVID-19 in vitro diagnostics listed by National Regulatory Authorities in IMDRF jurisdictions (18 May 2020) https://www.who.int/diagnostics_laboratory/200518_imdrf_collated_table_18_May_2020.pdf?ua=1 List of EUL products eligible for procurement https://www.who.int/diagnostics_laboratory/eual/listing/en/

Asia Pacific Medical Technology Association (APACMed)

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About APACMed

Founded in 2014, the Asia Pacific Medical Technology Association (APACMed) is the only regional association that provides a unified voice for the medical technology industry in Asia Pacific, representing over 140 suppliers and manufacturers of medical equipment, devices and in-vitro diagnostics, industry associations and other key stakeholders associated with the medical technology industry in Asia Pacific. The Association strives to promote innovation and impact policy that advances healthcare access for patients, and its mission is to continuously strive to improve the standards of care for patients through innovative collaborations among stakeholders to jointly shape the future of healthcare in the region.

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