CoRE Regulatory Perspective

Whither ASEAN regulatory agility and convergence in the ongoing COVID-19 pandemic?

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This essay describes health products regulatory agility and regulatory convergence in the context of ASEAN and COVID-19, the apparent challenge to convergence from member states' securing diverse vaccines for their own populations and why the pandemic may in fact reinforce convergence going forward.

The COVID-19 pandemic has seen a positive display of regulatory agility globally, regionally and nationally to facilitate the speedy development and emergency use authorisations (EUAs) of new diagnostics and vaccines. **Regulatory agility** refers to adoption of *risk-based, context-driven approaches* and *regulatory cooperation* based on *sound scientific evidence* and information. However, the roll-out of various vaccines in different countries and regions in 2021 poses a fresh set of challenges to the principles of regulatory cooperation that were instrumental in enabling regulatory agility during 2020.

This is exemplified within ASEAN as different member states undertake their own strategies for procuring and authorising a number of COVID-19 vaccines for their populations. Although the region's regulators have committed to harmonisation since the 1990s, pan-regional regulatory work-sharing and coordination of approvals for health products are still developing. However, the multi-route approach of ASEAN is arguably more appropriate under current circumstances for expediting procurement and EUAs of vaccines available for individual countries. This is when compared, for example, to the centralised European Union approach, which committed to procuring vaccines for all member states but has been criticised for slowness in securing supplies for Europe.

Convergence across ASEAN

Regulatory convergence[1] describes the *voluntary process* whereby regulatory requirements across economies become *more similar or aligned* over time through gradual adoption of internationally recognised technical guidance documents, standards and scientific principles and common or similar practices and procedures.

Reliance on decisions of trusted regulatory authorities is a critical aspect of convergence to avoid duplicative processes or delays in decisions by national regulators in different jurisdictions. The World Health Organization (WHO) promulgates Good Reliance Practices as a best practice to expedite access to safe, effective and quality medicines.

In the two decades prior to the COVID-19 pandemic, global regulators increasingly subscribed to and applied convergence and reliance. In ASEAN, the Pharmaceutical Product Working Group (PPWG) under the ASEAN Consultative Committee for Standards and Quality first convened national regulatory authorities (NRAs) in 1999 and over the intervening years, introduced regional common technical requirements and a common technical dossier. However, imposition of country specific regulatory requirements over the regional framework and lack of regulatory science proficiency, especially in smaller regulatory agencies, are constraints that need to be addressed.

[1] As defined in the APEC Regional Harmonisation Steering Committee's Strategic Framework

Convergence supports Regulatory Agility

Throughout 2020, regulatory agility became increasingly important around the world, including in ASEAN. Convergence and reliance enable regulatory agility, which includes applying non-traditional approaches while ensuring robust regulatory decision-making without compromising safety, quality and efficacy of innovative health products. This has been critical for timely EUAs of new COVID-19 vaccines developed at an unprecedented rate during 2020.

Fortuitously, a range of convergence platforms and frameworks were in place for rapid sharing of information and referencing more developed regulators' approaches at the start of the pandemic. These included international harmonisation initiatives by WHO and non-governmental associations like ICH[2] , the formation of the International Coalition of Medicines Regulatory Authorities (ICMRA) in 2014 and maturing of regional regulatory collaborative groupings like ASEAN's PPWG. From early 2020, ICMRA convened virtual seminars and working meetings to discuss regulatory considerations for COVID-19 clinical trials, therapeutics approvals, use of real-world evidence and information sharing to support EUAs of new vaccines.

Diversity of Vaccines

However, with new COVID-19 vaccines to expedite herd immunity becoming increasingly available, convergence of regulatory decision-making is being challenged by several political and socio-economic factors. These include vaccine nationalism, vaccine hesitancy and the fact that different vaccines with differing efficacy profiles are being used by countries within regions.

Across ASEAN, member states are procuring vaccines from different sources under separate agreements. Currently, three types of vaccines are being assessed or deployed across ASEAN - the newest mRNA technology vaccines (*Pfizer-BioNTech, Moderna*) and more traditional inactivated whole virus (*Sinovac, Sinopharm*) and non-replicating viral vector (*Oxford-AstraZeneca, J&J/Janssen, Sputnik V*) vaccines.

In the course of 2020, Singapore secured agreements for the *Pfizer-BioNTech*, *Moderna* and *Sinovac* vaccines ahead of any regulatory decision by the Health Sciences Authority (HSA), the country's national regulator. HSA granted interim emergency use authorisation for the Pfizer vaccine under its Pandemic Special Access Route on 14 Dec 2020 and for the *Moderna* vaccine on 3 Feb 2021 while it continues to review data for *Sinovac*. The national vaccination programme began on 30 Dec 2020 with the Pfizer product.

In other ASEAN countries, the main vaccines are the *Oxford-AstraZeneca* vaccine, with a significant amount produced by the Serum Institute of India, and the *Sinovac* and *Sinopharm* vaccines from China. From media reports as of 8 April 2021, Cambodia, Indonesia, Lao PDR,

[2] The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) brings together regulatory authorities and the pharmaceutical industry to discuss scientific and technical issues and develop ICH guidelines.

the Philippines and Thailand have planned or are rolling out vaccination programmes based on a combination of the AstraZeneca vaccine and one of the Chinese vaccines. Brunei and Malaysia are using the Pfizer product and the Sinopharm and Sinovac vaccines respectively, while Myanmar and Vietnam have started vaccinations with the AstraZeneca vaccine. The Philippines and Vietnam have granted EUAs for the Russian Sputnik V vaccine and Thailand for the J&J product. All ASEAN countries are eligible for vaccines through the COVAX[3] Facility.

Convergence Challenged and Reinforced

The diversity of vaccines and procurement agreements used by ASEAN member states apparently challenges convergence, with each country determining what works best for itself. However, the fundamental issue is more of urgent socio-political considerations taking precedence over regional regulatory cooperation.

This is understandable given the *lack of a pre-existing outbreak preparedness system* in the region when the pandemic took off in early 2020. Without such plans in place and with little initial global consensus on the nature and transmissibility of the SARS-CoV-2 virus, every country had to make quick public health decisions regarding issues such as border closures and implementation of lockdowns to safeguard their own populations. The extraordinary response of the international scientific community resulting in *rapid development of COVID-19 vaccines* within the pandemic's first year was not initially expected given the usually much longer development timelines for new vaccines.

It has not helped that *vaccine hesitancy and public concern about safety of new vaccines* are compounded by different country responses to adverse events temporally linked to new vaccines but for which causality is not established. For example, in early January 2021, the Danish Medicines Agency raised concern about a possible link of deaths in elderly to the Pfizer vaccine although this was subsequently ruled out by the European Medicines Agency (EMA). On the basis of available information and its adverse event response system, Singapore's HSA did not advise stopping immunisation with the Pfizer product.

In March 2021, concerns about blood clotting events linked to the AstraZeneca vaccine resulted in several countries temporarily halting vaccination as a precaution. At the time of writing, most countries have resumed use of the vaccine but several countries have recommended it only be used in specific age groups with strengthened advisories on this rare side effect. The WHO, EMA and other international experts have advised that the overall benefits of the vaccine outweigh its risks. In ASEAN where many countries are using the AstraZeneca product, Thailand and Indonesia initially delayed roll-out but have resumed use of the vaccine.

[3] COVAX is co-led by Gavi (a global public-private alliance with the goal of increasing access to immunisation in poor countries), the Coalition for Epidemic Preparedness Innovations (CEPI) and WHO. Its aim is to accelerate the development and manufacture of COVID-19 vaccines, and to guarantee fair and equitable access for every country in the world.

Even if a well-established regional convergence and reliance framework existed, national regulators would face difficulty in coordinating decisions due to *different degrees of risk-tolerance, trust and political sensitivity* within each country. This is exacerbated by vaccination roll-out based on EUAs and evolving real-world evidence, rather than full approval with safety and efficacy data over a longer period.

Regulatory convergence is therefore being challenged in the *immediate term* due to the rapidly developing scientific and socio-political issues linked to the speed of COVID-19 vaccines development, diversity of vaccines procured by different countries and lack of well-established, well-accepted regional regulatory referencing frameworks. However, the pressing urgency to respond in an agile manner to the pandemic and the vexing issue of new SARS-CoV-2 variants means that in the *near to medium term*, several of these factors could also support a regulatory convergence approach.

In particular, the rapidly evolving nature of scientific issues and information makes it untenable for ASEAN regulators, especially those with limited capacity, to respond in isolation to questions from political leaders and the public. Referencing and reliance on other trusted agencies is necessary for quick yet robust responses. Due to the long-standing links across ASEAN, information continues to be shared formally and informally among NRAs.

It is therefore likely that the enormous impact of this prolonged pandemic will see greater rather than less commitment to strengthen ASEAN's pandemic preparedness framework post-COVID-19. It is important for ASEAN to establish effective regional processes and structures in non-crisis times, which can be promptly activated during crises. Effective regulatory cooperation is a key aspect. While differing socio-political and cultural interests will persist, at the technical and scientific level, more effective and efficient regulatory convergence should be expected and strongly encouraged. This will ensure that Southeast Asia can better deal with future outbreaks and public health challenges.

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