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COMMENTARY

The COVID-19 crisis as an opportunity to strengthen global regulatory coordination for sustained enhanced access to diagnostics and therapeutics

Uttara Soumyanarayanan[1] | Mimi Choong[2] | James Leong[1] | Murray M. Lumpkin[3] | Guido Rasi[4] | John H. Skerritt[5] | Silke Vogel[1] | John C. W. Lim[1,6,7]

[1]Centre of Regulatory Excellence (CoRE), Duke-NUS Medical School, Singapore City, Singapore

[2]Health Sciences Authority (HSA), Singapore City, Singapore

[3]The Bill & Melinda Gates Foundation, Seattle, Washington, USA

[4]University Tor Vergata, Rome, Italy

[5]Department of Health, Canberra, New South Wales, Australia

[6]SingHealth Duke-NUS Global Health Institute (SDGHI), Singapore City, Singapore

[7]Consortium for Clinical Research & Innovation Singapore (CRIS), Singapore City, Singapore

Correspondence:
John C. W. Lim, Centre of Regulatory Excellence (CoRE), Duke-NUS Medical School, Singapore City, Singapore.
Email: john.lim@duke-nus.edu.sg

INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic presents an unparalleled opportunity for regulators globally to strengthen coordination, advance alignment initiatives, and exercise regulatory agility to facilitate access to the surge in diagnostics, therapies, and vaccines without compromising public safety. We describe international collaborative initiatives, summarize key experiences, and urge the global regulatory community to apply lessons from the current pandemic to strengthen and sustain cooperation for future public health emergencies and enhanced health products access.

As the pandemic continues, an enormous surge in global scientific research and development of COVID-19 diagnostics, therapies, and vaccines has occurred, including repurposing of existing medicines and new vaccines development. The need for regulatory agility and coordination among national regulatory authorities (NRAs) is more critical than ever to ensure that new health products can be expeditiously evaluated, while still ensuring their safety, quality, and efficacy.[1] An initial approach to instituting best pandemic regulatory practices has been advocated.[2] Ongoing assessments to approve vaccines from the growing number and diversity of candidates developed at great speed adds another layer of complexity to existing regulatory hurdles, such as lack of capacity and weak postmarketing surveillance especially in developing countries. In addition, developed and developing countries need to ensure equitable and appropriate access to these initially limited products based on health and societal priorities.

This unprecedented pandemic is therefore presenting an unparalleled opportunity for the international health products regulatory community to strengthen coordination, advance alignment initiatives, and implement effective reliance, referencing, and convergence processes that have been promoted by the World Health Organization (WHO), the International Coalition of Medicines Regulatory Authorities (ICMRA), and other regional fora since the turn of the century.

LEVERAGING ON LESSONS LEARNT FROM PAST PUBLIC HEALTH EMERGENCIES

Experiences from previous outbreaks influence current approaches to combatting this pandemic. In contrast to premature curtailment of previous outbreak vaccines efforts due to issues such as lack of suitable animal models, short-lived immunity, antibody-dependent enhancement and geographically localized cases, COVID-19 vaccine development timelines have accelerated at an extraordinary rate.[3] Lessons from past public health crises, notably the significance of communication and transparency among regulatory agencies, have aided in formulating strategies to deal with COVID-19 but are being adapted to the current unique regulatory context and challenges.

Although diverse healthcare systems and socioeconomic, political, and legal frameworks can pose significant barriers to coordinating many aspects of health care, including health products regulation, they are not insurmountable. During the Ebola outbreaks in Africa (2014–2016), the WHO convened meetings with regulators, involving many international consultations, to assess and expedite Ebola vaccine development and facilitate access.[4] Joint reviews of multiple vaccine candidates involving various committees reduced duplication of efforts, shortened approval timelines, and clarified roles and responsibilities of involved parties. Although Ebola and COVID-19 differ in magnitude and impact, geographically dispersed developed and developing nations are reviewing similar health products for COVID-19. In this context, collaborative multistakeholder engagement and coordination of regulatory efforts across national jurisdictions can enhance the speed, robustness, and credibility of regulatory decision making, potentially helping to address vaccine confidence issues.

EXPEDITING ACCESS TO HEALTH PRODUCTS THROUGH ENHANCED REGULATORY AGILITY

Regulatory agility, which refers to adoption of risk-based, context-driven approaches, and regulatory cooperation, is pivotal to achieving timely responses to public health emergencies. With quick and accurate diagnosis of COVID-19 active and past infections forming a critical component of managing this pandemic, NRAs around the world have already used such approaches for reviewing and expediting access to diagnostic test kits while further validation is conducted.[5]

Accelerated product development and marketing application review procedures are available but continue to require informative clinical and safety data from appropriately designed clinical trials. In some cases, time-limited conditional approvals require marketing authorization holders to provide additional data before proceeding and pending full approval. Importantly, effective postapproval vigilance monitoring systems to track and analyze adverse events in larger populations constitute a key requirement for approvals lacking routine comprehensive data sets, given the pandemic context in which benefit-risk decisions regarding these products are made. There are situations where differences in opinion may occur between NRAs and reference regulatory authorities. Even with commitment to regulatory cooperation, each jurisdiction's NRA must continue to make evidence-based decisions, supported by the latest science, local disease demographics and epidemiology, and health system capabilities. Hence, postapproval activities are a crucial responsibility of each NRA for the continual assessment of the benefit-risk balance of health products within the context of its own health system environment, in view of new updates or developments in supporting data, emergence of subgroup differences or potential influence of ethnicity. The success and soundness of expedited approvals requires effective product life cycle management by NRAs; this includes monitoring safety and effectiveness in a wider real-world population, effective distribution and supply chain management, and quality control.

Expedited regulatory approaches also require a context-driven interpretation of data for authorizing diagnostics and medical interventions, with NRAs applying new pandemic measures and standards to make informed, risk-based decisions. The US Food and Drug Administration (FDA)'s Coronavirus Treatment Accelerator Program provides extensive guidance to developers on development considerations, quality assessments, and available pathways. In order to expedite the review process, the European Medicines Agency (EMA) and other authorities allow rolling submission of data from the vaccines' clinical trials that enables regulators to review data in real-time and grant an emergency authorization if the data are satisfactory. These authorizations are conditional and demand further safety and efficacy data from post-authorization studies, to receive a full approval. Furthermore, the EMA's fast-track pathway reduces review times from 210 to 150 days or less, provided robust clinical evidence is presented, and is being applied for promising COVID-19 treatments.[6] In view of the pandemic, the EMA has also developed strategies and guidelines for conducting remote good clinical practice inspections and virtual evaluations.

Concurrently, authorities are working with global and regional initiatives to collaboratively engage in assessing therapeutics and vaccines, including coordinated approaches to regulatory decision making at both clinical trials oversight and marketing authorization levels. Over 100 countries are participating in the WHO initiated "Solidarity" randomized trials for evaluating repurposed drugs as potential COVID-19

treatments.[7] Although some countries may have different views and uses for treatments due to the scant preliminary data available, the coordination of large international trials through this initiative aims to shorten the time to generate robust clinical evidence for making better informed decisions. With only a handful of COVID-19 related treatments approved to date, it is premature to assess the effectiveness of these global regulatory coordination activities but optimism for such approaches remains high.

The FDA's Project Orbis, involving collaborative concurrent review of oncology products by international regulators to facilitate patient access, is a good example of regulatory coordination and convergence.[8] Its first action in September 2019 in conjunction with Australia's Therapeutic Goods Administration (TGA) and Health Canada (HC) just preceded the start of the pandemic. Since then, the ICMRA, established to provide strategic leadership and promote coordinated responses across international NRAs, has convened virtual seminars to discuss regulatory considerations for COVID-19 clinical trials, therapeutics approvals, and the use of real-world evidence.[9] Other transnational regulatory groupings, such as the Access Consortium (comprising the TGA, HC, Swissmedic, Singapore's Health Sciences Authority, and the United Kingdom's Medicines and Healthcare products Regulatory Agency) and the African Vaccine Regulatory Forum (AVAREF) provide avenues for joint clinical trial application reviews by promoting work-sharing and trust, facilitating managing high volumes of applications. The Asia-Pacific Economic Cooperation Life Sciences Innovation Forum is advancing efforts in regulatory convergence for review and approval processes, applicable to COVID-19 products.

STRENGTHENING REGULATORY COORDINATION VIRTUALLY

Whereas the pandemic has adversely impacted the entire world, technology—including the huge increase in online conferencing—has enabled much of the professional workforce to continue with their responsibilities. Travel restrictions have compelled researchers, industry professionals, and regulators to convene productive virtual meetings and conferences, leading to widespread, internationally connected gatherings with minimal resources.

The global cooperation of regulators that is so critical in helping to manage the COVID-19 pandemic has already yielded various positive benefits, with what will likely be a long-term paradigm shift in regulatory interaction and collaboration. For example, the ICMRA has been convening fortnightly regulator sharing sessions fostering discussions on best practices, policies for decision making, and continued assurance of support to agencies facing regulatory hurdles. The 2020 World Health Assembly (WHA) was conducted virtually for the first time, with health ministers discussing future measures to manage the pandemic. These meetings exemplify the power of virtual platforms in bringing together geographically separated authorities and experts in real-time to share, discuss, and determine strategies for timely and cost-effective decision making. This new approach to global coordination should be further developed and strengthened as part of the "new normal" for efficient and effective regulatory collaborative operations.

ADVANCING AND SUSTAINING MULTILATERAL REGULATORY COORDINATION

A multipronged approach fostering coordination and synergy among different stakeholders is essential to deal with the magnitude of the crisis. With nearly 200 vaccine candidates against severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) under development, the positive surge in collaboration to expedite sound regulatory decisions for effective health products will also have to extend beyond the scope of NRAs to ensure equitable access by the entire world population and mitigate against the vaccine nationalism. This will require strong global cooperation and political commitment to avoid a situation where only resource-rich countries have first access to new COVID-19 health products, especially vaccines. During the 2020 WHA, member states pledged to ensure equitable access to COVID-19 diagnostics, therapeutics, and vaccines, particularly for low and middle-income countries.[10] This significant international commitment must translate into dedicated and real follow-up to ensure the pandemic is effectively corralled. In tandem with ensuring equitable access, efforts to ensure public confidence in the safety and efficacy of vaccines are critical, given the diversity of candidates and accelerated timelines for their approvals.

Effective international regulatory coordination for evaluating health products is an essential aspect of public and global health. Working with all relevant stakeholders, a historic opportunity presents itself for the international regulatory community to significantly advance coordination and cooperation using new communication technologies and other experiences gained during the pandemic. Early and ongoing multilateral stakeholder engagements, virtual discussions among global regulators, and serious sustained adoption of reliance practices to enhance efficiency and robustness of collaborative decision making should become defining characteristics of the post-COVID international regulatory landscape. This will address not only the current COVID-19 crisis but also ensure that the world's healthcare systems are well prepared to manage access to novel diagnostics, therapies, and

vaccines that are safe, effective, and of good quality for both future public health emergencies and more routine medical challenges.

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