COMMENTARY

Global Challenges in Regulatory Capacity and Capability Building: Extrapolating Lessons Learned From the HSA

John C.W. Lim[1], Cheng-Leng Chan[2] and Andrew Green[1]

Every medicines and medical device national regulatory authority operates within finite resource constraints, with smaller agencies in low- and middle-income countries disproportionately affected. The Singapore Health Sciences Authority has been pragmatic and open to regulatory innovation, without compromising commitment to public health and science-based decision making. Its experiences and approach are described as a case study for eliciting principles that may be helpful to addressing challenges in global regulatory capacity development.

All medicines and medical device national regulatory authorities (NRAs) are charged with the responsibility of ensuring timely access of their populations to quality, safe, and efficacious health products. Regardless of the level of a country's economic development, population size, and healthcare status, every NRA always operates within the constraints of finite resources. However, lack of finances, technical and scientific capabilities, and organizational capacity are resource-scarcity problems that disproportionately affect smaller NRAs in low- and middle-income countries.

Beyond the difficulties of providing adequate regulatory functions, as defined by the World Health Organization (WHO),[1] lack of resources also restricts NRAs in their efforts to do the following:

- effectively implement guidelines nationally from regional and international harmonization initiatives;
- develop skills to work effectively with stakeholders in government, industry, academia, patient advocacy groups, and nongovernmental organizations;
- optimize regional and global networks for greater collaboration and work sharing; and
- determine the appropriate scope and approach for regulatory innovation.

Singapore's experiences in addressing issues of regulatory capacity may be a useful reference for other countries. A former British colony, Singapore is an island city-state in Southeast Asia with a resident population of 5.6 million. Singapore became an independent republic in August 1965.[2] It was then a third-world country, but over the past half century, it has experienced remarkable growth to become one of the most developed economies in the world today.

The regulation of health products evolved in tandem with the development of Singapore's healthcare system, which is recognized as one of the best in the world.[3] Before the mid-1970s, the focus of regulation was preventing illegal supplies of poisons and curtailing misleading advertisements. The enactment of the Medicines Act of 1975 provided a comprehensive regulatory framework for the control of medicinal products. Regulation progressively developed beyond enforcement by the Ministry of Health (MOH), through expanded responsibilities of the National Pharmaceutical Administration in the late 1990s, until the Health Sciences Authority (HSA) was established as a statutory board of the MOH in 2001. The HSA is a multidisciplinary agency that, in addition to regulating health products, also runs Singapore's national blood service and provides national forensic and analytical chemistry expertise. Under the HSA, national regulatory functions for medicines and medical devices were initially performed by three centers that later merged to form the Health Products Regulation Group (HPRG) in 2006, following which the scientific capabilities for the full range of regulation in an era of rapidly advancing biomedical science developed quickly. However, given Singapore's size and human resource limitations, there has always been openness to adopting innovative regulatory approaches because it is not tenable to just keep increasing manpower.[4]

ADDRESSING REGULATORY CAPACITY CHALLENGES

Key approaches adopted by the HSA to address capacity challenges demonstrate

[1]Centre of Regulatory Excellence, Duke-National University of Singapore Medical School (Duke-NUS), Singapore, Singapore; [2]Health Products Regulation Group, Health Sciences Authority, Singapore, Singapore. Correspondence: John C.W. Lim (john.lim@duke-nus.edu.sg)

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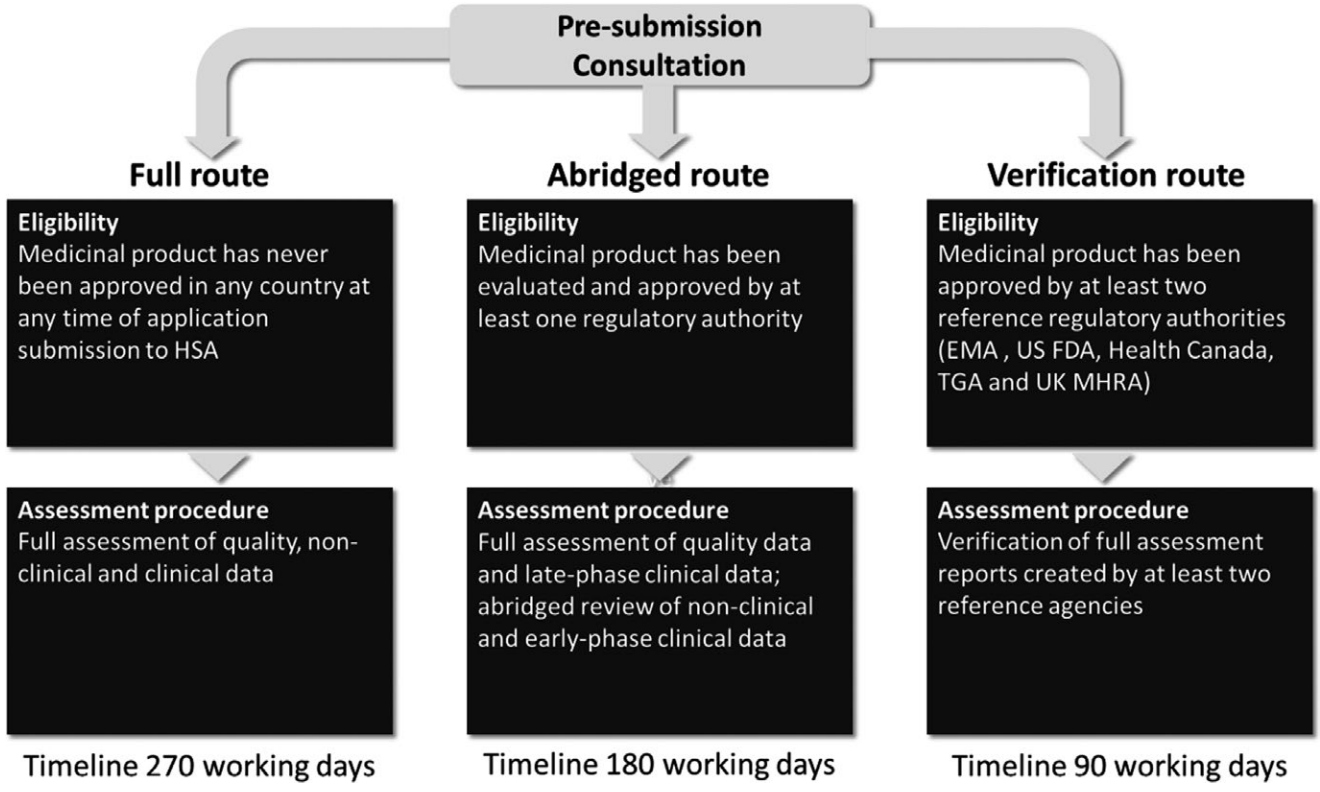

Figure 1 Singapore Health Sciences Authority's model for confidence-based stratification of marketing authorization application and evaluation of new medicines. The reference regulatory authorities are the European Medicines Agency (EMA), US Food and Drug Administration (FDA), Health Canada, Australian Therapeutic Goods Administration (TGA), and UK Medicines and Healthcare Products Regulatory Agency (MHRA).[6,8]

pragmatism and receptivity toward regulatory innovation, without compromising the fundamental commitment to safeguard public health and make decisions based on sound scientific principles.

Confidence-based regulatory approach

The HPRG currently has about 300 staff members dedicated to regulating medicines, medical devices, and other health products, such as complementary medicines and cosmetics. Although this is considered relatively well resourced in South-East Asia, it is small compared with the large, well-established NRAs of the United States, the European Union, and Japan.[5] Since the HSA was established, there has been a commitment to using accelerated or facilitated regulatory pathways that leverage on marketing authorization decisions made by other trusted NRAs, in line with the principles of reliance and recognition advocated by WHO.[6,7]

The HSA is recognized as the first NRA to formally codify and implement a three-tier review strategy comprising the *full*, *abridged*, and *verification* routes illustrated in **Figure 1**.[6] This approach streamlines marketing authorization applications for new medicinal products. Those that have not been licensed elsewhere undergo full review, whereas products previously approved by other NRAs can be evaluated through the faster and less-burdensome abridged or verification review routes.[8] Full evaluation comprises ≈5% or less of medicines licensed by the HSA but is important in providing a full range of marketing authorization options. Most products approved by the HSA go through the abridged (≈85%) and verification (≈10%) routes. A similar confidence-based tiering approach has also been adopted for medical devices.

Singapore's regulatory approach that can rely on prior decisions by other trusted NRAs enables flexibility in allocating resources to premarket authorization review of new medicines, while allowing jurisdictional sovereignty for locally relevant benefit–risk decisions.[6,9] This confidence-based system promotes transparency of submission and evaluation routes without compromising the robustness of the HSA's authorization decisions.

Risk-based regulatory framework

Medicines and medical devices in Singapore are regulated under the Health Products Act, a risk-based legislative instrument enacted in 2007 to supersede the Medicines Act.[4] The new act places most of the key details for regulating different product categories in the subsidiary legislation. This permits greater flexibility to calibrate regulation according to degree of product risk and facilitates faster response and adjustment without requiring parliamentary approval for changes to the main act. In an era in which new clinical data on the use of medicines are generated at unprecedented rates, such risk-based legislation enables regulation to promptly adjust to updated benefit–risk assessments.

Regulatory collaboration with international partners

In the early 2000s, when Singapore began heavily investing in biomedical research

and development, it was recognized that the HSA needed the capability to conduct full evaluation for first-in-world products. The Centre for Drug Evaluation, which later became part of the HPRG, was established with a small team of in-house expertise and a large panel of external experts so that full dossier evaluation of medicines could be performed when required.

The HSA has been actively engaged in international regulatory collaboration, including supporting harmonization and convergence initiatives. Strategic memoranda of understanding and confidentiality agreements with overseas partners enable the agency to practice reliance and recognition by leveraging relevant scientific decisions made overseas. In the area of medicines, it has work-sharing arrangements through a regulatory consortium established in 2007 with Australia's Therapeutic Goods Administration, Health Canada, and SwissMedic.[9]

The HSA has also been an active member of harmonization working groups in the Association of South-East Asian Nations (ASEAN), including leading the ASEAN Sectoral Mutual Recognition Agreement on Good Manufacturing Practice Inspection of Manufacturers of Medicinal Products. It is a founding member of the International Coalition of Medicines Regulatory Authorities. The HSA became a member of the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) in 2017 and was nominated into its management committee in June 2018.[10] By playing an active role in regional and international regulatory harmonization, the HSA can influence the development of regulatory science and keep abreast of best regulatory practices and policy.

Embracing smart regulation

Aligning with Singapore's broader national imperatives, the HSA practices "smart regulation" to find a good balance between safeguarding public health and facilitating access to innovative therapies. The agency is always open to exploring innovation in regulatory frameworks, including appropriate use of adaptive licensing for cell, tissue, and gene therapies and "regulatory sandboxes" in areas of unmet medical need.

PRINCIPLES

The experience of the HSA is intimately tied to Singapore's context. Nonetheless, the authors believe that using the HSA as a case study, the following principles could help address resource challenges faced by both developing and developed countries in strengthening regulatory capacity and capability:

Define a clear understanding of benefit–risk and the scientific rationale for product categorization when refining regulatory systems

This allows appropriate risk-based allocation of resources to premarket and postmarket activities and informs the optimal design and adoption of assessment templates and legislative instruments.

Prioritize capacity development in areas of expertise guided by a country's needs

At the rate new health products are being launched and globalized, NRAs should actively pursue collaboration to optimize scarce resources. Rather than duplicating the full spectrum of premarket authorization expertise for product categories in every jurisdiction, regional regulatory strengthening could be achieved more effectively through increasing adoption of reliance, referencing, and work sharing, as advocated by the WHO.[7] NRAs that realistically assess their needs and focus on relevant areas of capacity building are more credible partners in regulatory groupings and when establishing memoranda of understanding and confidentiality agreements.

Be open to regulatory systems innovation

Although market accessibility of sophisticated innovative products, such as gene therapy, has yet to become a priority in many countries, the availability of such products heavily drives improvement in standards of care. However, accommodating scientific breakthroughs requires new regulatory paradigms, including approaches such as real-world evidence for decision making. Regulators who are adaptable are pivotal to ensuring that regulatory systems remain relevant, public health is safeguarded, and socioeconomic development is promoted.

Be actively engaged in international harmonization and convergence initiatives

Such collaborations nurture mindsets and skills to understand which regulatory activities should be done by NRAs at the national level (e.g., pharmacovigilance and enforcement) and what could be achieved through regional and global cooperation with associated reliance and work sharing for premarket authorization decisions. This is especially pertinent when addressing rapidly developing fields, such as cell, tissue, and gene therapies.

The international regulatory environment is complex and continuously evolving. Its many stakeholders, if engaged positively and appropriately, can become partners in collectively promoting sound and robust regulation of medicines and medical devices. Strong ongoing commitment by NRAs to risk-based regulation, relevant capacity development, systems innovation, and global collaboration is critical. We hope that Singapore's experience may be helpful in supporting enhancement of global regulatory capacity and systems in the face of resource constraints.

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CONFLICT OF INTEREST

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