



A COVID-19 Emergency Response Strategy
**Establishing Domestic Vaccine Development
Capacity During a Public Health Emergency**

July 2021

Task Force for Promoting Pharmaceutical and
Medical Device Regulatory Harmonization in Asia

Executive Committee on Global Health and Human Security

A COVID-19 EMERGENCY RESPONSE STRATEGY **Establishing Domestic Vaccine Development Capacity During a Public Health Emergency**

Recommendations for the Grand Design for Asian Pharmaceutical and Medical Device Regulatory Harmonization

Task Force for Promoting Pharmaceutical and Medical Device Regulatory
Harmonization in Asia
Executive Committee on Global Health and Human Security

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1. Introduction

More than a year has passed since the World Health Organization (WHO) declared the SARS-CoV-2 (COVID-19) outbreak a pandemic. COVID-19, however, has yet to be contained, resulting in more than 150 million confirmed cases and 3 million deaths worldwide. Advances in science and technology have made it possible to develop vaccines never before used in humans by leveraging innovative technologies, and large-scale vaccination efforts are now underway around the world. However, as SARS-CoV-2 variants emerge, there is concern about a resurgence of cases.

In Japan, which has recorded more than 600,000 confirmed cases and 10,000 deaths [as of May 2021], the spread of variants is causing a steady increase in the numbers of both new cases and deaths. To combat the pandemic, the government has placed priority on vaccinations, and the Japanese people also have high expectations in this area. Nonetheless, at this moment, Japan is not only lagging behind Europe and the United States, but in fact has one of the lowest vaccination rates in the world. The reason for this is that Japan has to import all the COVID-19 vaccines it needs because the country has made little progress in either developing domestic vaccines or manufacturing foreign-developed vaccines domestically. Consequently, not only is Japan significantly behind other countries in vaccinating its own people, but its inability to contribute to the global community in a manner expected of a country that is a leader in science and technology has gravely damaged its international reputation and standing.

Facing the variant-driven fourth wave, Japan urgently needs to develop domestic vaccines so that it can protect people from possible fifth and sixth waves and reduce the risks to its national interests and security that are inherent in having to leave its people's lives entirely in the hands of other countries. Under the "Accelerated Parallel Plan" for vaccine development, the Japanese government has been funding pertinent R&D and manufacturing systems. The reasons why those efforts have failed to lead to domestic vaccine development must be examined, and a framework must be created that ensures that funding for R&D and other activities will result in the implementation of domestic vaccine development.

The Japanese government has been working with other Asian countries and regions to establish the infrastructure for clinical development and promote regulatory harmonization in the fields of pharmaceuticals, medical devices, and regenerative medicine products (hereinafter, "pharmaceuticals and medical devices"; including the reorganization and enhancement of the international operations of Japan's Pharmaceuticals and Medical Devices Agency, or PMDA, to achieve these). The ultimate goal is to improve patient access to pharmaceuticals and medical devices and to advance universal health coverage (UHC) in Asian countries and regions, in accordance with both the Grand Design for Asian Pharmaceutical and Medical Device Regulatory Harmonization and its implementation strategy (approved by Japan's Headquarters for Healthcare Policy on June 20, 2019, and July 14, 2020, respectively). Despite having originally been devised to cover a variety of diseases, these measures are also of great significance in terms of achieving domestic vaccine development during the current pandemic.

Developing domestic vaccines, however, involves various steps, ranging from basic and applied research to clinical trials, regulatory approval, manufacturing, and distribution. Improving just one of these areas will not serve the original purpose if progress is impeded in any of the other steps. What is needed is to redouble domestic and international efforts to improve each step and, when doing so, to incorporate into policies both push and pull incentives to develop domestic vaccines. Another important point in this endeavor is that, given the serious impact the current pandemic is having on people's lives and on society as a whole, the Japanese government must consider the viewpoint of the general public and ensure that policies earn people's trust and give them peace of mind. International collaboration and cooperation are also essential. In light of these factors, the Task Force calls once again, as it has in previous recommendations, for greater efforts to achieve regulatory harmonization in the fields of pharmaceuticals and medical devices and to establish the infrastructure for clinical development. Moreover, with regard to measures to develop domestic vaccines, the Task Force has formulated a COVID-19 Emergency Response Strategy based on the perspective of regulatory science that aims for scientific rationality and societal harmonization.

2. COVID-19 Emergency Response Strategy

(1) Emergency regulatory approval process and international regulatory harmonization

(a) Emergency regulatory approval process for domestic vaccines

With regard to emergency regulatory approval, Japan already has a special approval system in place, and in fact, Pfizer's COVID-19 vaccine was approved under this system. The problem is that, because the system requires pharmaceuticals to have been evaluated and granted distribution approval by the authorities of a country whose pharmaceutical system is at a level equal to that of Japan (i.e., European countries, the United States, or other countries specifically designated by a cabinet order), the system is not applicable to domestic vaccines if they are deployed in Japan ahead of other countries. Consideration should therefore be given to revising Japan's regulatory approval process for times of emergency, as opposed to the normal process, so as to enable the development not only of domestic vaccines, but also of innovative domestic therapeutics during crises such as the current COVID-19 pandemic.

(b) Need to assess efficacy and safety based on international regulatory harmonization

Even in times of emergency, it is necessary to ensure that pharmaceuticals have demonstrated a certain level of efficacy and safety based on scientific evidence. This is particularly important for vaccines, which are expected to be given to tens or hundreds of millions of healthy individuals and need to be administered in a way that also earns people's trust and gives them peace of mind. Hence, even under emergency use authorization programs in the West—including the US Emergency Use Authorization (EUA) system—large-scale phase 3 clinical trials are being carried out for COVID-19 vaccines with the participation of tens of thousands of people to verify efficacy in preventing symptomatic infection. (Note that, while allowing for speedy decision-making through efficacy and safety assessment based on the results of an interim analysis of the phase 3 clinical trials, the US EUA and other systems mandate that even subsequent to the emergency use authorization being granted, the clinical trials must continue through to the final analysis; in other words, the implementation of clinical trials is not shortened.)

Yet, assessments of the efficacy and safety of vaccines—that is, determining whether the benefit outweighs the risk—in times of emergency can change dynamically depending on the state of the pandemic. Thus, a more rational approach to assessment should be explored, especially in light of the accumulation of evidence from foreign vaccines already in use. In fact, Japan's Ministry of Health, Labour and Welfare (MHLW) has already indicated in a

notification¹ that with regard to the approval process for COVID-19-related pharmaceuticals, etc., there is some degree of flexibility even under the existing system. Namely, if the results of a publicly funded research project confirm that a pharmaceutical has demonstrated a certain level of efficacy and safety, that may constitute reasonable grounds not to submit materials on the results of clinical trials, and this applies to vaccines as well.² In cases where a certain level of evidence has been accumulated with regard to the relationship between immunogenicity and efficacy of foreign vaccines already in use, another conceivable approach is, for example, to grant approval after confirming a certain level of safety and efficacy based on the results of clinical trials on immunogenicity, and then confirm efficacy further using real-world data. In such cases, the decision must be made based on international regulatory harmonization. This is essential to ensure that domestic vaccines are recognized by the international market as global public goods from a worldwide perspective and to gain trust from the people of Japan. At international forums such as the ICMRA³ and WHO, discussions are now underway, gathering wisdom from all over the world and pursuing scientific truth in order to achieve a more dynamic and ambitious approach to scientific evidence that addresses pandemics. In these discussions, it is absolutely essential that Japan play a leading role in building an international consensus by actively collaborating with European and US authorities, and that the internationally agreed upon results be reflected in Japan's domestic approval criteria. In doing so, it is also important to facilitate communication among industry, government, and academia concerning international trends and Japan's approach to the approval process with a view to giving companies greater predictability in their clinical development projects. By taking these measures, the government should swiftly advance regulatory harmonization that contributes to achieving domestic vaccine development.

(c) Issue to address going forward

As mentioned above, no matter what the system, confirming a certain level of efficacy and safety based on an approach that is harmonized with international standards must be a prerequisite. In addition, the issue to address moving forward is what the regulatory approval process should be in emergency situations. The Japanese government as a whole

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1. The May 12, 2020, notification concerning the handling of COVID-19-related pharmaceuticals, etc. in approval evaluations, issued jointly by the director of the Pharmaceutical Evaluation Division and the director of the Medical Device Evaluation Division, of the MHLW Pharmaceutical Safety and Environmental Health Bureau (PSEHB/PED Notification No. 0512-4 and PSEHB/MDE Notification No. 0512-1).
 2. Response given by the director-general of the Pharmaceutical Safety and Environmental Health Bureau at a meeting of the House of Councillors' Committee on Health, Welfare and Labour on May 14, 2020.
 3. International Coalition of Medicines Regulatory Authorities. A forum aimed at promoting international collaboration in the field of pharmaceutical regulation, participated in by the senior executives of pharmaceutical regulatory authorities of about 30 countries and regions in Asia, Europe, the Americas, and elsewhere. Japan currently serves as vice-chair.

must immediately consider this issue as part of its broader debate on the legal system for the overall response to emergencies and should look to the example of how other countries have responded during this pandemic.

(2) Promotion of clinical development

Although Japan was a vaccine powerhouse in the 1980s, the last time it developed and launched a domestic vaccine was in 1995. In this time of emergency, and from the perspective of national security too, it is safe to assume that the people of Japan have high expectations for the domestic vaccine and biopharmaceutical industry. From the public's perspective as well, now is the time to strengthen Japanese companies' vaccine development capabilities—especially, clinical development capabilities—and to rebuild the foundation for the future growth of the biopharmaceutical industry. Toward that end, the government of Japan must provide support for domestic companies and academic institutions that do not have experience in leading large-scale multiregional clinical trials so that they can overcome various obstacles. Specifically, it is imperative to consider the initiatives listed below and start with those items that are achievable.

(a) Promote multiregional clinical trials

International standards require that clinical trials for a COVID-19 vaccine include a confirmatory phase 3 clinical trial. This requirement must be met without delay.

As it is difficult to conduct large-scale phase 3 clinical trials in Japan in which tens of thousands of people participate to verify efficacy in preventing the onset of the disease, in order to establish the infrastructure needed to conduct clinical trials compliant with the ICH-GCP (Good Clinical Practice of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use) at core clinical research hospitals in other Asian countries and regions—as called for in the Grand Design for Asian Pharmaceutical and Medical Device Regulatory Harmonization—and enable Japan-led multiregional clinical trials to be conducted in a speedy manner, it is essential that the Japanese government strongly promote the establishment of a clinical research and trial network in Asia through Japan Agency for Medical Research and Development (AMED)-funded projects. Specifically, efforts need to be accelerated to train clinical trial support staff, prepare manuals, and deploy equipment and materials needed to conduct clinical trials at individual research hospitals. In doing so, consideration should be given to promoting more effective and efficient support by strengthening cooperation with AMED grants, such as by using official development assistance to deploy equipment and materials at overseas institutes, and by working with the Asian Development Bank and other international development finance institutions. Moreover, in light of the increasing importance of multiregional research in the field of health and medicine, the government should consider clearly identifying support for multiregional research as one of AMED's activities. Even after the network is created, its functionality can be maintained in a systematic and reliable

manner by utilizing the network and its constituent sites in normal times, for example, to conduct clinical trials for vaccines against infectious diseases that are prevalent overseas, so that the network can deal with pandemics and other emergencies. Furthermore, efforts should be made to create an intergovernmental network to facilitate the introduction of products in participating countries after clinical trials are completed, and to utilize the PMDA's Asia Training Center for Pharmaceuticals and Medical Devices Regulatory Affairs to enhance understanding of pharmaceutical regulations.

(b) Pursue clinical development as a national strategy

To advance government-wide initiatives as part of a national strategy, the Cabinet Secretariat's Office of Healthcare Policy should spearhead the strengthening of collaboration between relevant ministries—the Cabinet Secretariat; MHLW; Ministry of Education, Culture, Sports, Science and Technology; Ministry of Foreign Affairs; and so on—and pertinent organizations including the PMDA, AMED, National Institute of Infectious Diseases, and National Center for Global Health and Medicine. In addition, to ensure that the government initiatives work in practice, collaboration and cooperation among industry, government, and academia should be enhanced, especially through the promotion of personnel exchanges and close communication between the strongly motivated industrial sector and the intellectually inquisitive academic community. Domestic vaccine candidates to be funded by the government must be selected through rigorous scientific assessment under a fair and transparent process.

(c) Accelerate the harmonization of clinical trial design and assessment methods

As the administration of already-approved foreign vaccines progresses, it is becoming increasingly difficult to conduct placebo-controlled clinical trials. Under these circumstances, approaches to clinical trial design and assessment methods going forward (e.g., active-control non-inferiority clinical trials, adaptive trials, or interim analyses and other methods for assessing clinical trials) should be dynamically harmonized and adjusted through discussions at international forums, taking into account a variety of conditions, such as the status of the spread of the infectious disease, progress on administering vaccinations, and scientific advances. In particular, the Japanese government should lead the way on harmonizing and coordinating discussions that are currently underway at the ICMRA, WHO, and other international forums on finding a more dynamic and ambitious approach to scientific evidence to address pandemics.

(d) Promote vaccine development as a global public good

Vaccines are global public goods, and even for Japan, which has introduced the Asia Health and Wellbeing Initiative and claims to be a nation built on science and technology, it is a major undertaking to carry out well-prepared multiregional clinical trials in Asia that

produce successful results and that take into consideration exit strategies including market development. Multiregional clinical trials, even for a single candidate vaccine, are likely to cost approximately ¥50–100 billion. It is essential to prepare the business plan at an early stage, consider the characteristics of each vaccine, identify the candidates through rigorous assessment, and then proceed to development.

3. Future Government-Wide Initiatives and Systems

Japan should view the current situation as an opportunity to strengthen domestic capabilities to develop vaccines, both as preparedness in normal times and as preparation for possible emerging and reemerging infectious diseases in the future. At the same time, the nation must devise measures to maintain its domestic capabilities in the areas of biopharmaceutical R&D, clinical development, and manufacturing during normal times as part of its vision for the vaccine and biopharmaceutical industry in the 21st century.

In addition, it is crucial to the effective implementation of the measures described in this strategy that the relevant ministries come together to carry them out as government-wide initiatives, working to coordinate and strengthen systems across ministerial boundaries. This issue is presently being discussed at the Headquarters for Healthcare Policy's council on pharmaceutical development, and based on those conclusions, practical actions should be taken through close industry-government-academia cooperation. In tandem with that, the budget needed to implement these actions should be secured.

The pandemic facing the world today poses a whole host of global health issues relating to preparation for emerging and reemerging infectious diseases. Among the most pressing is how to swiftly develop and supply vaccines and therapeutics for those diseases. This challenge, however, can no longer be addressed by a single nation; it is essential that the international community work together. Japan as well must therefore create the necessary systems as part of such an international response and cooperation. The series of strategies represented by the Grand Design for Asian Pharmaceutical and Medical Device Regulatory Harmonization has been formulated to present specific initiatives to be undertaken by Japan in order for the country to contribute to addressing global health issues in Asia. These recommendations are based on the efforts made thus far and summarize measures that must be further accelerated as a "COVID-19 Emergency Response Strategy." It is hoped that the implementation of these recommendations will enable the Japanese government to meet the people's expectations by improving its emergency response and that it will contribute to the achievement of UHC in Asian countries and regions.

Task Force for Promoting Pharmaceutical and Medical Device Regulatory Harmonization in Asia

In December 2018, the Task Force for Promoting Pharmaceutical and Medical Device Regulatory Harmonization in Asia was created under the Executive Committee on Global Health and Human Security. It is comprised of nearly two dozen experts from industries, academia and government. Japan is committed to promoting universal health coverage (UHC) as part of its contribution to the global health field, but as Asia undergoes economic expansion, population increases, and the aging of its societies, the inadequate access in the region to pharmaceuticals and medical devices—including products that utilize innovative technologies—poses a serious obstacle to that objective. In 2019, the first phase of the task force’s work culminated in a proposal, “Recommendations on Formulating a Grand Design for Asian Pharmaceutical and Medical Device Regulatory Harmonization—A Four-Wheel Drive Approach to Promoting Regulatory Harmonization in Asia,” which was published under the name of EC. In 2020, in order to encourage the implementation of the Japanese government’s Grand Design for Asian Pharmaceutical and Medical Device Regulatory Harmonization, which was announced in June 2019, the task force published another recommendations "A UHC Approach to Harmonizing Asian Pharmaceutical and Medical Device Regulations" that proposed to promote the development of clinical trials and clinical research systems based on the needs of Asian countries.

Executive Committee on Global Health and Human Security

The Executive Committee on Global Health and Human Security is a high-level, public-private platform that facilitates the Japanese government’s policymaking on global health and public-private collaboration in that field. Under the chairmanship of Professor Keizo Takemi, the committee holds quarterly meetings to provide a venue for unofficial exchanges of views and information-sharing among senior representatives from government ministries, academia, private companies, and civil society organizations in Japan. Relevant global health experts are invited to speak at the meetings to offer their knowledge and advice. The committee is an integral part of the Global Health and Human Security Program of the Japan Center for International Exchange (JCIE), which manages all aspects of the committee’s work.

Japan Center for International Exchange (JCIE)

Founded in 1970, JCIE is one of Japan’s leading foreign policy institutes. With offices in Tokyo and New York, it organizes legislative exchanges and policy dialogues that bring together key figures from diverse sectors of society, both in Japan and overseas. During the 1990s, it played a leading role in encouraging the adoption of human security as a pillar of Japanese foreign policy, and this led to the launch of a series of major initiatives on global health. The Friends of the Global Fund, Japan, was created in 2004, the Global Health and Human Security Program in 2008, and the Healthy and Active Aging in Asia in 2017 to strengthen public-private partnership and Japan’s role in global health.

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* Representatives from the Office for Healthcare and Medical Strategy of the Cabinet Office, Ministry of Health, Labour and Welfare (MHLW), and Ministry of Foreign Affairs (MOFA) also joined the meetings.

* The Task Force members acknowledge and agree that this recommendation was compiled independently from any business transactions and decisions in relation to the supply or purchase of goods or services from specific member companies and that the provision of support has in no way influenced the content.

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