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

Executive Committee on Global Health and Human Security

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1. Introduction

Since the Headquarters for Healthcare Policy of Japan established the Basic Principles of the Asia Health and Wellbeing Initiative (AHWIN) in July 2016, the initiative has been endorsed by many countries, prompting the start of concrete partnerships and projects. At the same time, however, there was awareness that a number of themes and issues had not been addressed in the Basic Principles. In view of that, the Basic Principles were revised in July 2018, taking into account the Liberal Democratic Party's recommendations on the promotion of AHWIN. The revised Basic Principles refer to pharmaceuticals, medical devices, and regenerative medicine products (hereinafter, "pharmaceuticals and medical devices"), declaring, "In order to contribute to resolving the 'drug lag' between Japan and Asia, Japan will promote harmonization efforts to make pharmaceutical approval systems and safety regulations more effective and rational by ensuring interoperability in Asian countries of data used for approval of pharmaceuticals."

Japan has committed to promoting universal health coverage (UHC) as part of its contribution to the global health field. In other Asian countries, however, the access to pharmaceuticals and medical devices—including products that utilize innovative technologies—is insufficient, posing a serious issue. To date, Japan has participated in international regulatory harmonization initiatives, incorporating the outcomes to eliminate its drug and device lag. Such international regulatory harmonization initiatives will play an important role in improving access to pharmaceuticals and medical devices in other Asian countries/regions as well. Based on this belief, the Japan Center for International Exchange (JCIE), under its Executive Committee on Global Health and Human Security, created a Task Force for Promoting Pharmaceutical and Medical Device Regulatory Harmonization in Asia that is made up of experts from industry, academia, and government. With a view to improving access to pharmaceuticals and medical devices in Asia, the task force has held a series of discussions on a grand design for regulatory harmonization and relevant matters, the result of which is reflected in the following recommendations.

2. The Significance of Formulating a Grand Design

Asian countries/regions that are presently undergoing remarkable economic and population growth are expected to face a rapid aging of their societies in the near future, just as Japan has experienced. This is bringing drastic changes to the environment surrounding pharmaceuticals and medical devices. Given that improving access to these

products in individual Asian countries/regions is expected to contribute to better health among the people of Asia as a whole, active efforts should be made on this front from the perspective of advancing UHC. Now is the time to examine this issue from the viewpoint of the patients who can benefit from these products and to develop a borderless Asian market for pharmaceuticals and medical devices that enables the high-quality pharmaceuticals and medical devices approved in one country/region to be approved and swiftly made available to patients in other countries in Asia.

Meanwhile, as the industry globalizes and products diversify, regulatory regimes for pharmaceuticals and medical devices become increasingly complex and sophisticated, making many regulatory authorities worldwide realize the importance of international cooperation. In Asia, too, a growing number of countries/regions are working to build pharmaceutical regulatory regimes that are in tune with international standards, accompanied by an increasing desire to introduce innovative pharmaceuticals and medical devices. At the same time, there is heightened interest in cost-effective, quality products, driven by concerns about the financial burden and its impact.

Access to pharmaceuticals and medical devices is a complex issue that entails a variety of intertwined factors, ranging from research and development to regulation and the securing of intellectual property. Addressing these issues requires a Japanese nationwide effort—one in which industry, academia, and government must closely cooperate.

These circumstances suggest that Asian countries/regions have an urgent need to harmonize their regulations for pharmaceuticals and medical devices, develop human resources for the regulatory authorities, and build development structures for the relevant infrastructure and systems. The objective should be to create an Asian ecosystem conducive to better access, thereby achieving a healthy longevity society in the future. Toward that end, a grand design that contains the elements listed below should be formulated in order to concentrate the efforts of industry, academia, and government in a way that is accountable to civil society.

3. Initiatives for Better Patient Access to Pharmaceuticals and Medical Devices

(1) Basic Approach

Shared principles and values

The human and material resources at the disposal of each Asian country/region are limited. Accordingly, they should promote healthcare based on social values—i.e., healthcare that is assessed in terms not only of its contributions to better patient outcomes at a lower cost, but also to improvements in labor productivity and to the economy of the society as a whole−while at the same time aiming to achieve rational medicine, whereby patients are provided with optimal treatment that takes into account the latest scientific knowledge. Regulations grounded in science, or in other words, regulatory science,[1] can serve as the common language as we seek to promote this type of health and medical care. Although

[1] Japan's *4th Science and Technology Basic Plan* defines regulatory science as "science for coordinating results of S&T [science and technology] with the most desirable form for harmony between people and society by conducting accurate forecasts, assessments, and decisions based on evidence for the purpose of using the results of S&T for the people and society."

regulatory science is at the core of pharmaceutical and medical device regulations, the notion is not yet well understood in Asia. Steps therefore need to be taken to increase the understanding and application of regulatory science.

Close cooperation that respects the position of regulatory authorities in other Asian countries/regions

The regulatory authorities of each country/region are responsible for contributing to the health of the people by making effective pharmaceuticals and medical devices swiftly available to the public while ensuring the safety of these products. Japan's regulatory authorities have forged ties with their counterparts in other Asian countries/regions in a spirit of mutual respect and equal partnership, and must build upon those ties to promote further cooperation. During that process, the utmost priority should be given to developing the human resources needed in each country/region. In particular, it is important to utilize the human-resource development programs being carried out by Japan's Pharmaceuticals and Medical Devices Agency (PMDA) at the Asia Training Center for Pharmaceuticals and Medical Devices Regulatory Affairs, for example, to deepen the understanding of Japanese regulations as a means to lay the foundation for regulatory harmonization in Asia.

Coordination and cooperation with the business community's activities

Regulatory harmonization requires understanding and cooperation not only on the part of those imposing regulations, but also on the part of the business community that is subjected to the regulations. Hence, regulatory authorities and business communities need to work together by coordinating their respective activities.

Taking infrastructure development into consideration

Conventional initiatives for things like regulatory harmonization have focused primarily on the aspect of "soft" elements, such as human-resource development to train the diverse personnel needed both in government agencies and in other sectors related to pharmaceutical regulations, as well as regional platforms and meetings that enable the debate and information-sharing to promote regulatory harmonization. However, to enable Asian countries/regions to make cutting-edge pharmaceuticals and medical devices available to the public quickly, it is also necessary to develop the infrastructure, especially for the clinical trial phase onward, through "hard" approaches, including the establishment of clinical trial sites. These "hard" and "soft" approaches need to be made in a balanced manner.

(2) Measures Package

(i) Establish systems and frameworks

- Japan should take the lead in organizing an "Asian network meeting," comprised of the heads of national regulatory authorities, which could serve as a platform for regulatory harmonization and other activities in Asia. It would be preferable for the regional offices of the World Health Organization (WHO) contribute to the meeting and maintain a close relationship.
- To facilitate joint responses to issues shared by Asian countries/regions, Japan should endeavor to create a regional environment conducive to public-private cooperation

and partnerships, such as by supporting the business community's efforts—a good example of which is the Asia Partnership Conference of Pharmaceutical Associations (APAC) spearheaded by the Japan Pharmaceutical Manufacturers Association.

- Japan must consider surveying and assessing the needs of each Asian country/region for pharmaceuticals and medical devices and creating a framework in which the stakeholders—mainly the business community—utilize such information. This should be pursued in cooperation with Japan's diplomatic missions to these countries/regions and the Japan External Trade Organization (JETRO), as well as with overseas regulatory authorities when needed.
- To further strengthen collaboration with other Asian countries/regions, Japan should consider increasing its workforce, including placing staffers dedicated to various priority countries/regions, in the PMDA. Furthermore, Japan should consider personnel exchanges, such as one in which officials engaged in regulating pharmaceuticals and medical devices would be dispatched from or invited to Japan upon request from the government of another country/region. At the same time, consideration should be given to utilizing the existing frameworks of and collaborating with the Japan International Cooperation Agency (JICA).
- Entities implementing these measures should always be mindful of ensuring transparency and accountability vis-à-vis civil society and should endeavor to provide information proactively.

(ii) Establish clinical trial systems

- It is often the case that the use of highly innovative pharmaceuticals and medical devices in the post-market phase is spread from clinical trial sites to other facilities. Thus, establishing clinical trial sites for highly innovative pharmaceuticals and medical devices can result not only in accumulating useful evidence based on clinical trials, but also in improving access to post-market pharmaceuticals and medical devices. In view of these benefits, Japan should help other Asian countries/regions establish clinical trial sites that are in line with the international technical standards.
- To that end, the Japanese government should examine the options available for financing other Asian countries/regions to build the necessary infrastructure. Those options may include loans from the Asian Development Bank (ADB) or the World Bank Group, as well as the use of the Economic Research Institute for ASEAN and East Asia (ERIA). Consideration also needs to be given to making these options function organically through JICA projects, among other possibilities.
- To enable Asian countries/regions to generate higher-quality clinical evidence on their own, Japan should consider helping develop not only medical practitioners but others involved in clinical testing—e.g., clinical biostatisticians, clinical research associates (CRA), clinical research coordinators (CRC)—in partnership with academic institutions and other stakeholders.
- When delivering medical devices and regenerative medicine products to other Asian countries/regions, there will be cases where the manual skills required to handle them must be provided at the same time. Therefore, in the capacity building of clinical trial sites, priority should be placed on those in need of technology transfer.
- When creating these systems to implement clinical trials, the Asian countries/regions concerned must first examine the matter on their own. Japan, while drawing on its

experience to date, must respect these countries'/regions' deliberations and ownership of the process as they help them build their systems.

(iii) Promote regulatory harmonization

- The PMDA's Asia Training Center for Pharmaceuticals and Medical Devices Regulatory Affairs and other programs should be leveraged to urge other Asian countries/regions to incorporate international standards and norms.
- The concept of "Reliance"[2] is promoted by the WHO, and Japan should collaborate with the WHO to encourage other Asian countries/regions to recognize this concept. The permeation of the concept is expected to lead to the creation of a borderless Asian market.
- What is needed, in addition to enhancing regulations, is human resource development, namely the capacity building of regulatory authority officials engaged in inspection, quality control surveys, reliability studies, and post-market safety measures. Furthermore, to provide more effective training on biopharmaceuticals and other advanced products in the future, training plants operated and managed by academic institutions should be utilized.
- As improved access to innovative pharmaceuticals and medical devices needs to accompany post-market safety measures, Japan should help other Asian countries/regions to build their capacities in devising better safety measures and sharing safety information. It also should play a leading role in creating a framework for utilizing real-world data (RWD) in Asia, which includes the perspective of improving an environment for collecting and managing data and ensuring data quality.

(iv) Priorities in individual fields

Pharmaceuticals

- Recent years have seen an increasing number of pharmaceutical development projects that utilize multiregional clinical trials, participated in primarily by Japanese, US, and European entities. Given that a large percentage of the world's population lives in Asia, the region's contribution to such multiregional projects would accelerate pharmaceutical development. Pharmaceuticals particularly in need of active development are those for diseases common in Asia, such as hepatitis, stomach cancer, and infectious disease, along with those for dementia and other diseases expected to become more prevalent with the aging of the region's population. To advance the development of these products, the necessary foundations must be laid, especially by harmonizing regulatory requirements for pharmaceutical development and creating clinical trial networks based on specific areas of diseases for the purpose of increasing joint clinical trials in Asia and thereby improving access at a faster pace.
- With respect to generic drugs, other Asian countries/regions have high expectations for the quality products made in Japan. As such, these drugs represent a field in which great benefits can be gained from internationally harmonized guidelines. Toward that end, Japan should first participate actively in projects aimed at developing

2 *Reliance* in this context means that, when a regulatory authority of one country/region conducts approval reviews or inspections, they consider, attach importance to, and utilize in their regulatory activities, the outcomes of assessments made by their counterparts in other countries/regions.

internationally standardized guidelines. Based on that outcome, they should thereafter endeavor to disseminate those guidelines to other Asian countries/regions.

- As for over-the-counter (OTC) drugs, as Asian countries are becoming increasingly health conscious, the high quality and other benefits of the products made in Japan are attracting considerable interest, and it is expected that the demand for Japanese OTC drugs is likely to rise further. In that context, the Self-medication Collaborative Asian Regulator Expert Roundtable (Self-CARER)[3] should be utilized to facilitate more vigorous exchanges of views with the aim of raising health awareness and improving access in Asia.
- A pharmacopoeia is a fundamental element in setting a country/region's quality standards for pharmaceuticals. As such, standardizing and harmonizing pharmacopoeias would eliminate duplicate testing. In view of that, Japan should carry out initiatives and exchanges of opinion in order to encourage both harmonization with the Japanese Pharmacopoeia and the use of it as a reference for the pharmacopoeias of other Asian countries/regions. Considering that traditional herbal medicines are widely used throughout Asia, it is particularly important to cooperate in setting standards for the safety of crude drugs.

Medical devices and in vitro diagnostics

- Given the different medical environments and diversity of the medical devices in Asia, it is difficult to adopt a single, uniform approach to Asia as a whole. It is therefore essential to take a systematic approach by first surveying the needs of each country/region, then designing policies based on the findings on a field-by-field basis.
- ASEAN member states and others are currently working to increase consistency among national regulations for medical devices. Japan should support this process to help them establish regulations that are in line with the international efforts to harmonize medical device regulations.
- Attention should also be paid to a report published by the Japanese Ministry of Health, Labour and Welfare's Health Science Council on December 25, 2018. Compiled by the Council's subcommittee on pharmaceutical and medical device regulations as a summary of the revisions to the Pharmaceuticals and Medical Devices Act and relevant systems, this report indicates the direction of initiatives to develop innovative medical devices efficiently. Specifically, it points out medical devices' feature of being constantly and continuously improved and enhanced, as well as the emergence of the new types of medical devices that take advantage of big data, artificial intelligence, and other revolutionary technologies. In light of these, the report recommends that the approval system be rationalized to make it applicable to these medical devices, and that testing and assessment systems be developed that enable the evaluation of the effectiveness and safety of those devices. Japan needs to implement these systemic improvements and share the latest knowledge obtained with other Asian countries/regions.

[3] The Self-medication Collaborative Asian Regulator Expert Roundtable, or Self-CARER, is a forum in which regulatory authorities in the Asia-Pacific region work together to harmonize regulations for OTC drugs.

Regenerative medicine products

- In recent years, the development of regenerative medicine products in Asia has been progressing rapidly. As the markets and the regulatory regimes for these products are expanding, the field of regenerative medicine products is at a crucial stage for creating globally accepted regulatory regimes in Asian countries/regions. Having established a conditional and time-limited approval system, Japan leads the world in the area of regulating regenerative medicine products and should therefore help the rest of Asia to develop quality controls and other regulations. This should be achieved by comparing the Japanese system with those of other Asian countries/regions while taking into account the unique characteristics of regenerative medicine products, such as their heterogeneity and the strict conditions for their transport. Efforts should also be made to introduce safety evaluation tests and other tools throughout Asia based on regulatory science.

By simultaneously implementing the measures described above, Japan should aim to create a multilateral environment conducive to other Asian countries'/regions' acceptance of its approval and inspection results and its regulatory regime.

4. Looking Ahead

These recommendations identify and address the matters requiring consideration at present. Given the constantly changing international environment, however, additional responses may present themselves, and those should be incorporated and pursued as well.

Asian countries/regions vary in terms of their levels of medical services, maturity of healthcare systems, and processes for decision making. It is thus essential for measures to be implemented in a manner suitable for the situation of the partner country/region. Industry-academia-government collaboration should serve as the engine for such initiatives. They should be steered and guided by dialogue and partnership between the governments of Japan and the partner countries, which together should serve as the front wheels, while the business communities of both countries should work as the rear wheels. By seamlessly combining all of these forces like a four-wheel drive vehicle, Japan should proactively help other Asian countries/regions improve access to pharmaceuticals and medical devices in an effective and organic manner.

Appendix: Members of the Executive Committee on Global Health and Human Security

Chair:	
Keizo Takemi	Member, House of Councillors; Senior Fellow, Japan Center for International Exchange (JCIE)
Director:	Akio Okawara, President and CEO, JCIE
Senior Advisors:	
Ichiro Aisawa	Member, House of Representatives
Katsunobu Kato	Member, House of Representatives
Yasuhisa Shiozaki	Member, House of Representatives
Norihisa Tamura	Member, House of Representatives
	(alphabetical order)
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Motohisa Furukawa	Member, House of Representatives
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Naoki Ikegami	Professor, Graduate School of Public Health, St. Luke's International University
Sumie Ishii	Chairperson, JOICFP (Japanese Organization for International Cooperation in Family Planning)
Keisuke Isogai	Director-General, Research Promotion Bureau, Ministry of Education, Culture, Sports, Science and Technology (MEXT)
Hiroto Izumi	Special Advisor to Prime Minister
Masamine Jimba	Professor, Department of Community and Global Health, Graduate School of Medicine, University of Tokyo
Yasushi Katsuma	Professor, International Studies Program, Graduate School of Asia-Pacific Studies (GSAPS); Head of Global Health Affairs & Governance Group, Institute for Global Health Policy (iGHP), the National Center for Global Health & Medicine (NCGM)
Kiyoshi Kodera	Chair of the Board, Water Aid Japan
Norihiro Kokudo	President, National Center for Global Health and Medicine
Tatsuya Kondo	Chief Executive, Pharmaceuticals and Medical Devices Agency (PMDA)
Kiyoshi Kurokawa	Professor Emeritus, Tokyo University; Professor Emeritus, National Graduate Institute for Policy Studies; Chairman, Health and Global Policy Institute Japan
Mari Michinaga	Chairperson, Japan Medical Association
Asahiko Mihara	Member, House of Representatives
Takashi Miyahara	Deputy Director-General, International Bureau, Ministry of Finance
Nobuyuki Morishima	Vice President and Representative Director, Otsuka Pharmaceutical Co.
Haruo Naito	President and CEO, Eisai Co., Ltd.; Vice President, Japan Pharmaceutical Manufacturers Association (JPMA)

Yasuhide Nakamura	Professor, School of Nursing and Rehabilitation, Konan Women's University; President, WHO Association of Japan
Hiroki Nakatani	Project Professor, Senior Researcher, Keio Global Research Institute (KGRI), Keio University
Shigeru Omi	President, Japan Community Healthcare Organization (JCHO); Regional Director Emeritus, World Health Organization for Western Pacific Region
Yohei Sasakawa	Chairman, Nippon Foundation
Atsushi Seike	President, The Promotion and Mutual Aid Corporation for Private Schools of Japan; Executive Advisor for Academic Affairs, Keio University
Johtaro Seki	President, International Total Engineering Corporation (ITEC)
B.T. Slingsby	Executive Director and CEO, Global Health Innovative Technology Fund (GHIT)
Hideo Suzuki	Director-General for Global Issues, Ministry of Foreign Affairs (MOFA)
Yasuhiro Suzuki	Medical Commissioner, Ministry of Health, Labour, and Welfare (MHLW)
Yukio Takasu	United Nations Under-Secretary-General for Management
Isao Teshirogi	President and CEO, Shionogi & Co., Ltd.
Takao Toda	Vice President for Human Security and Global Health, Japan International Cooperation Agency (JICA)
Chikara Tsukamoto	Councillor, Cabinet Secretariat; Director-General, Office for Pandemic Influenza and New Infectious Diseases Preparedness and Response, Office for Ebola Virus Diseases Preparedness and Response, Coordination Office of Measures on Emerging Infectious Diseases, Cabinet Secretariat
Taizo Yakushiji	Research Counselor, Institute for International Policy Studies; Program Director, Science and Technology Research Partnership for Sustainable Development, Japan Science and Technology Agency
Kenji Yasukawa	President and CEO, Astellas Pharma Inc.

International organizations: Bill & Melinda Gates Foundation, United Nations Children's Fund (UNICEF), United Nations Development Programme (UNDP), United Nations Population Fund (UNFPA), UN Women, World Bank Group, and World Health Organization Centre for Health Development (WHO Kobe Centre)

* The Task Force for Promoting Pharmaceutical and Medical Device Regulatory Harmonization in Asia that was organized under this committee consisted of Tatsuya Kondo (Chief Executive, PMDA; Task Force Chair); Keizo Takemi (Executive Committee Chair); Akio Okawara (Executive Committee Director); representatives from the Office for Healthcare and Medical Strategy of the Cabinet Office, MHLW, MOFA, the Federation of Pharmaceutical Manufacturers' Associations of Japan (FPMAJ: Hirofumi Inoue, Masaaki Takeyasu), the Japan Pharmaceutical Manufacturers Association (JPMA: Haruhiko Hirate, Masaomi Akana), and the Japan Federation of Medical Devices Associations (JFMDA: Akira Kuba); as well as Hiroshi Kasanuki (University Professor and Adviser, Waseda University Medical Regulatory Science Institute), Hiroki Nakatani,

and Daikichi Monma (Member, Board of Directors, Global Health Innovative Technology Fund). The Task Force was administered by JCIE with support from the JPMA.

The members of the EC and TF 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 have in no way influenced the content.

Executive Committee on Global Health and Human Security

The Executive Committee on Global Health and Human Security is a 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 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.

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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