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MINI-REVIEW

Adoption of Regulations for Cell Therapy Development: Linkage Between Taiwan and Japan

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Although cell-based therapy has become a promising treatment, its practice and evaluation process remain unstandardized. Therefore, Japan initiated a dual-track regulatory framework for cell-based therapy aiming to promote and regulate the therapies to ensure that patients can access safe and effective treatments. Influenced by such pathway, Taiwan adopted the framework and initiated its own cell-based therapy regulation in 2018. This paper discusses how Japan has influenced Taiwan in developing regulations for cell-based therapy.

DUAL-TRACK REGULATORY FRAMEWORK

Potential breakthroughs in cell-based therapy are eagerly anticipated and expected because of possible cures for unmet medical needs. However, the cell-based products have nonuniform characteristics because of biological heterogeneity. The efficacy, safety, and cost-effectiveness evaluations of cell-based therapy may be difficult than that of conventional pharmaceutical treatments. Assurance of the product quality and confirmation of the therapy effectiveness would be difficult in the conventional regulatory framework for pharmaceuticals or medical devices in Japan.[1] Another major issue is the challenge to safeguard patients, including foreigners (called medical tourism), who seek for the daily practice of using unapproved cell therapy products in private clinics, resulting in serious adverse events.[1–3] To accelerate and regulate the practical applications while maintaining the safety of the therapy, a dual-track regulatory framework for cell-based therapy has been officially revealed in Japan on November 25, 2014.[1–4] The dual-track regulatory framework has two approaches of introducing the cell-based therapy to patients. The Act on the Safety of Regenerative Medicine (ASRM) promotes the use of cell-based therapy in hospitals and clinics. The other is Pharmaceuticals, Medical Devices, and Other Therapeutic Products Act (PMD Act), which promotes the development and manufacture of products by industry.[1–3]

The Act on the Safety of Regenerative Medicine covers the field of previous ethical guidelines for noncommercial clinical research as well as daily practice using unapproved cell-based products, such as cancer immunotherapy. This act does not cover the clinical trials that aimed to authorize the cell-based products for marketing.[1–3,5] The PMD Act covers clinical trials that aimed to authorize the cell-based products for marketing. In the PMD Act, regenerative medical product (RMP) is defined as a distinct product category separate from pharmaceutical and medical devices. Under the new act, there are two ways to authorize the commercialization of RMPs. The first way is the same as the conventional authorization system for pharmaceuticals and medical devices. However, the conventional authorization process is not feasible for some of the RMPs because of their biological heterogeneity. The second way is a conditional and time-limited marketing authorization system that may be applied to certain RMPs, provided the safety of the products is ensured and the efficacy of the products is assumed through small-scale clinical trials.[1–3,6] This dual-track regulatory framework represents an attempt by Japan to promptly deliver cell-based therapy to patients and accelerates the adoption of innovative technologies while ensuring the efficacy, safety, and reduced processing cost of the cell-based application.

Based on this framework, Japan has been making greater efforts to cooperate with foreign regulatory authorities, industries, and academia, with an intention to develop this regulatory framework as a standard that can be used internationally or, at least, in Asia.[4] Influenced by the dual-track regulatory pathway, Taiwan subsequently built a new framework for cell-based therapy in July 17, 2018, becoming the first nation to adopt the framework from Japan. Particularly, the revised version of the Administrative guidelines for the implementation of Medical Devices and Specific Medical Technology, which is also called Special Regulation for Cell Therapy, came into effect on September 6, 2018.[7] Similar to the Japanese ASRM, the Special Regulation for Cell Therapy governs the technology for the clinical use of cell-based and tissue-based therapies among doctors. Moreover, similar to the PMD Act of Japan, the Act on the Management of Regenerative Medical Preparations, which is currently in legislation in Taiwan, will review and approve the manufacture, commercialization, and selling of cell-based products. By sharing technology information and regulatory experience, Japan plays an important role in influencing Taiwan in building regulations for cell therapy (**Figure 1**). To explore

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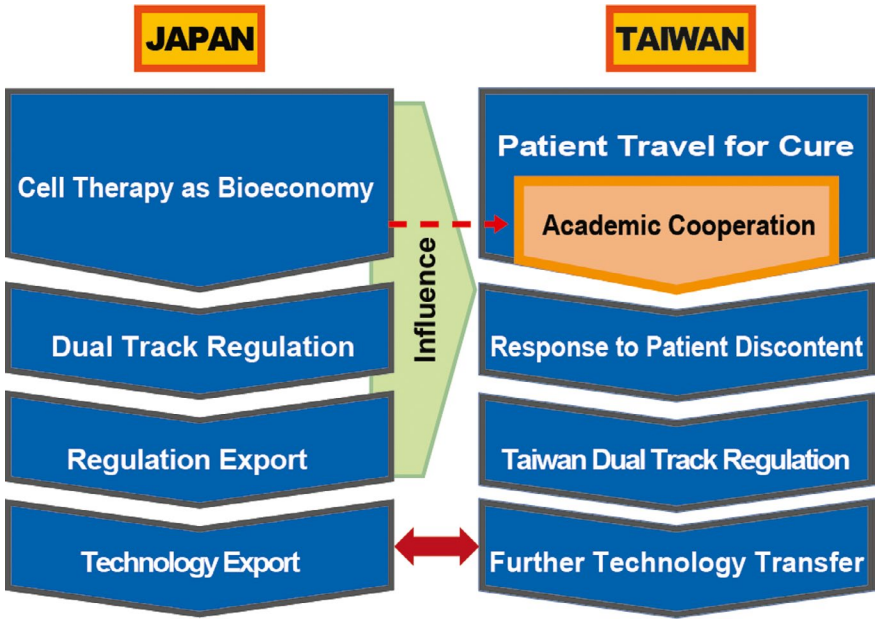

Figure 1 How Japan influenced Taiwan in building a dual-track regulatory framework for cell-based therapy. With the increasing daily practice of using unapproved cell therapy products and the increase in medical tourism, Japan launched dual-track regulations for the related fields, hoping to strengthen its bio-economy by exporting the framework and technology. Influenced by Japan and based on the requirement of domestic patients, Taiwan subsequently built a framework for cell-based therapy and became the first nation to adopt the framework from Japan.

the interaction between the two countries, this paper discusses how Japan influences Taiwan on the development of regulations in the cell-based therapy sector.

PATIENTS' DEMAND

Patients' demand for new treatment serves as the key point for triggering a change in the current regulatory system. In Taiwan, the option for lawful cell-based therapy for unmet medical needs is limited. Therefore, the number of patients who are seeking cell-based therapy through Japan has been increasing.

In 2013, Caspar Wang, who was a nasopharyngeal carcinoma patient, traveled to Japan to receive immune cell therapy. Fortunately, he achieved complete remission from cancer after receiving the therapy.[8] In October 6, 2015, eager to help more patients with cancer, Caspar Wang launched a petition on the Policy Network Participation Platform, which is a website under the National Development Council, to call on the Taiwanese government to legalize immune cell therapy in Taiwan.[8] There was an immense response, which made the Taiwan Ministry of Health and Welfare (MOHW) to face these unmet medical needs.

Later, one accident accelerated the legalization of cell therapy in Taiwan. In 2015, a water park (Formosa Fun Coast) explosion caused 510 patients to sustain burn injuries, leading to a shortage of skin transplantation at that time. With the help of autologous cell therapy products from Japan, patients with severe burn injuries recovered smoothly.[9] The occurrence of this incident highlighted the need for stem cell therapy and required a change in the current regulatory system in Taiwan.

ACADEMIC ADVOCACY AND POLICY ADOPTION

Since 2003, Taiwan biomedical scientists developed their interests in the field of cell therapy. However, without a clear regulation that governs cell therapy in Taiwan, the developers encountered difficulties in applying for any permission from the government for clinical research, evaluation, or application of cell-based treatment. In 2013, Akihiro Shimosaka and Yao-Chan Chen co-hosted the fourth annual conference of the Asian Cellular Therapy Organization (ACTO) in Taiwan, with an aim to address the issues on cell therapy regulation and application, and to learn experience from Japan. The Taiwan Food and Drug Administration officials were invited to join that event. Through this conference, the officials realized that the progression of cell therapy has advanced by leaps in Japan, South Korea, and other Asian countries.

Correspondingly, in 2014, Yao-Chan Chen, the founder of the Taiwan Association for Cellular Therapy, helps to build a strong connection between the Taiwanese and Japanese governments. After understanding the advantages of a dual-track regulatory framework, the MOHW started planning a dual-track regulatory framework for cell therapy in Taiwan.

With the help of the ACTO, Taiwanese authorities visited several cell-related industries and regulatory agencies, including the Pharmaceuticals and Medical Devices Agency (PMDA) and Ministry of Health, Labour, and Welfare (MHLW), in Japan. The two governments had the chance to exchange their regulatory experiences. Taiwan built a new cell-based therapy approval process called Special Regulation for Cell Therapy, similar to the Japanese ASRM. According to this regulation, any hospital or clinic that wishes to operate cell

therapy must submit to the MOHW for approval with the treatment plan and clinical trial-related data (e.g., preclinical data, clinical trial reports, or published papers).

IMPLICATIONS

The realization of the value of advanced cell-based therapy and its related technology highly depends on the regulatory system. Based on the Special Regulation for Cell Therapy, Taiwan has approved 21 cell-based therapy technologies within 10 biotechnology companies that can be used in 14 hospitals (until February 2020). The new regulation is accelerating a safe and fast provision of innovative products to patients with intractable diseases.

Because Japan is thought to be the pioneer and leader in cell-based therapy technology and in establishing the related regulations, Taiwanese biotech companies and health providers are keen to learn the technology from Japan, including J-TEC, CellSeed, Hitachi, Tella, Kurume University, Chiba University, etc… To perform cell therapy in Taiwan, hospitals cooperated with the industry to transfer the technology from Japan. With the help of the Special Regulation for Cell Therapy, the technology transfer between Taiwan and Japan has become more immense.

As an advanced technology, cell therapy posts an uncertainty for physicians, in the aspect of effectiveness and liability. Likewise, insufficient information and knowledge can hinder patients from distinguishing the effective cell therapy from others. To promote cell therapy in Taiwan, the government needs to create a platform for its lawful use and allow medical institutions and patients to find the cell therapy technology and information that they need. This platform also drives the demand for cell therapy technology in the Taiwanese market.

The previous trends in the regulatory experiences from other countries can serve as a good point for governments to follow. Similar to Taiwan, China is considering on building related regulations on cell therapy. On March 29, 2019, in China, a public hearing was held that aimed to emulate the system of the Special Regulation for Cell Therapy of Taiwan.[10]

In conclusion, the cooperation between Japan and Taiwan highlights the benefit of promoting regulatory development and technology in the medical sectors across countries. With the help of Japan, Taiwan can develop and promote cell therapy effectively. On the other hand, by sharing regulatory experience and transferring technology, Japan can enhance the attractiveness of its medical technology and encourage local and foreign investment in biomedical industries, thereby further boosting the country's economic growth.

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