GLOBAL PERSPECTIVES

New Regulatory Framework for Medical Devices in Japan: Current Regulatory Considerations Regarding Clinical Studies

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ABSTRACT

In Japan, a recent issue that required an urgent response was the streamlining of regulations concerning clinical trials of medical devices. On July 31, 2017, the Ministry of Health, Labour and Welfare enacted a new regulatory framework called the fast-break scheme for innovative medical devices aiming to expedite patient access while reducing the premarket regulatory burden of clinical trials and enhancing postmarketing commitments. The new framework is expected to provide greater benefits to patients who require access to new medical devices and to companies via improved transparency and predictability, as well as to reduce the social and medical cost incurred for medical innovation.

ABBREVIATIONS

FDA = Food and Drug Administration, MHLW = Ministry of Health, Labour and Welfare, PMDA = Pharmaceuticals and Medical Devices Agency

During the past decade, the Japanese government has been committed to expediting the medical device review process to secure timely access to innovative and safe devices for patients. The review time for new medical device regulatory approval in Japan has been dramatically shortened, from an average review time of 21.1 months in 2005–2008 (1) to a 60th-percentile review time of 10.1 months in 2015 (2), providing better predictability of market launch for sponsor companies. In addition, the difference in timing between regulatory approvals in the United States and Japan for the same devices (hereafter "device lag") has nearly been resolved as a result of several government policy initiatives (3). Examples of recent policies include the SAKIGAKE Designation System (4), which corresponds to US medical device "breakthrough therapy designation" described in the 21st Century Cures Act (5,6); and "Harmonization by Doing" (7) between the US Food and Drug Administration (FDA) and the Japanese authorities to facilitate global clinical trials.

Medical expenditures have been increasing in Japan concomitantly with the rapidly aging population, and, in response to this issue, the Principles for Drug Pricing Reform were agreed to by the Health Policy Related Ministers in December 2016. The key principles were (*i*) maintaining universal health care coverage, (*ii*) promoting medical innovations, (*iii*) mitigating public burden, and (*iv*) improving quality of medical services (8). In line with these principles, in January 2017, the Pharmaceuticals and Medical Devices Administration of the Ministry of Health, Labour and Welfare (MHLW) of Japan presented regulatory policies to meet three objectives: (*i*) enhance patient access to medical innovation, (*ii*) promote regulatory reform to reduce the social cost of medical services, and (*iii*) promote appropriate use of medical technologies to improve the quality of medicine (9). One of the issues that required an urgent response was the streamlining of regulations concerning clinical trials of medical devices.

In the medical device development and review process, one of the bottlenecks is the requirement to conduct clinical trials in Japan, particularly for devices developed and approved in foreign countries. Therefore, device lag still remains in certain therapeutic categories in which the extrapolation of foreign clinical data to the Japanese medical setting is needed for

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Japanese regulatory approval. A recent example was EXCOR (Berlin Heart, Berlin, Germany), a pediatric external ventricular assist device, which is the same as the ventricular assist device for children approved in 2011 in the United States (10). An additional clinical trial was required to demonstrate extrapolation of the clinical benefit and safety indicated by the foreign data to the Japanese medical environment. Even with its small sample size, the additional clinical trial in Japan before premarket application resulted in 4 years' delay of device approval in Japan compared with the US approval. Therefore, the clinical trial policy in Japan needed to be improved to respond urgently to unmet medical needs by enabling timely patient access to innovative high-risk medical devices.

FAST-BREAK SCHEME FOR INNOVATIVE MEDICAL DEVICES

On July 31, 2017, MHLW launched a new regulatory framework called the fast-break scheme for innovative medical devices to expedite patient access (11). MHLW has also launched new regulatory guidance on clinical trials of medical devices. MHLW and Pharmaceuticals and Medical Devices Agency (PMDA) noted that the FDA has also been discussing pre- and postmarketing balance of medical devices regulations in a product life cycle (12), considering the advantages and drawbacks of traditional trial versus real-world evidence (13). In particular, the 21st Century Cures Act redefines the clinical evidence required to demonstrate the benefit and safety upon which approval of high-risk devices is based to include case studies, registries, and articles in the medical literature, rather than only more rigorous clinical trials (14). Indeed, the FDA recently approved a supplement expanding the indication of Sapien 3 transcatheter aortic valve replacement (Edwards Lifesciences, Irvine, California) to include valve-in-valve procedures based on real-world data from the Transcatheter Valve Therapy Registry, which contains records of transcatheter aortic valve replacement procedures in more than 100,000 patients, of whom 600 received off-label valve-in-valve procedures (15). Moreover, real-world data from Japanese postmarketing surveillance (16) supported the FDA's approval of an expansion of the indications for the Zilver PTX device (Cook Medical, Bloomington, Indiana) (17), which was the first approved drug-eluting stent for the femoropopliteal artery.

MHLW and PMDA have found several cases in which randomized double-blind clinical trials were extremely difficult to perform because of a limited number of potential patients. In these cases, if PMDA required robust clinical evidence, as would occur for review of pharmaceutical agents, this would lead to a tremendous delay in patient access to innovative medical devices for the treatment of diseases for which no standard alternative treatment is currently available.

The fast-break scheme is a system to approve innovative medical devices in Japan for which a medical need exists in an expedited manner at an earlier stage of development, based on clinical evidence not confined to rigorous prospective randomized controlled trials, but including other adequate clinical data reasonably likely to predict clinical benefit and safety (case studies, registries, and clinical research) based on a limited patient population in certain clinical settings. However, the scheme is to be applied only to brand-new medical devices that satisfy the following criteria: (*i*) there are no appropriate alternative medical devices or there is a reasonable likelihood of greater efficacy and safety compared with existing products; (*ii*) the target patient population is affected by life-threatening disease or serious disability in daily life; (*iii*) some supporting clinical evidence is available; (*iv*) there is a postmarketing commitment to an appropriate risk-management plan in collaboration with relevant academic medical societies (eg, sales restriction to certified experts and institutions) and rigorous real-world evidence collection and evaluation; and (*v*) there is justification of difficulty in conducting a new prospective clinical trial. MHLW and PMDA will consult with sponsors and relevant medical societies to determine whether a candidate device meets the criteria for the fast-break scheme.

After premarket applications are filed, PMDA will start the process according to the scheme to review the existing clinical evidence predicting clinical benefit and safety (including case studies, registries, and clinical research), as well as postmarketing commitments, including a risk-management plan. At the time of approval, the sponsor is required to present a risk-management plan supported by the relevant academic medical societies and to collect real-world evidence as a postmarketing commitment (**Fig**). Under the risk-management plan, sales will be restricted to certified experts and institutions capable of performing "rescue" treatment in cases of emergency. During the postmarketing commitment, the sponsor may expand the number of approved institutions if the postmarketing data indicate a better outcome compared with predetermined criteria, as in the case of the first absorbable coronary scaffold, Absorb GT1 (Abbott Vascular, Santa Clara, California), approved in November 2016 in Japan (18). Further, the sponsors will be able to use the longer-term outcomes of the device to expand the indications from those based on, for example, surrogate endpoints.

JUSTIFICATION OF THE FAST-BREAK SCHEME IN THE CLINICAL CONTEXT

As described earlier, MHLW emphasizes securing timely patient access to innovative medical devices in an expedited manner in response to unmet medical needs. Medical devices are of various kinds, have a wide range of modes of use, and are more invasive compared with fixed-dosage forms of pharmaceutical agents. The clinical evaluation takes into account these device-specific characteristics, such as difficulty in setting control arms in clinical trials of invasive devices from a bioethical perspective. Recent debate in the field of epidemiology, taking account advances in medical information communication technology with universal coverage of patient records, indicates that retrospective cohort comparative studies can be a powerful tool to evaluate