Citation: Clin Transl Sci (2020) 13, 877–879; doi:10.1111/cts.12784

MINI-REVIEW

A Concept for a Japanese Regulatory Framework for Emerging Medical Devices with Frequently Modified Behavior

Nagomi Ota[1], Keisuke Tachibana[1], Tetsuya Kusakabe[2], Shoji Sanada[2] and Masuo Kondoh[1,*]

Recent progress in the Internet of Things and artificial intelligence has made it possible to utilize the vast quantity of personal health records, clinical data, and scientific findings for prognosis, diagnosis, and therapy. These innovative technologies provide new possibilities with the development of medical devices (MDs), whose behaviors can be continuously modified. A novel regulatory framework covering these MDs is now under discussion in Japan. In this review, we introduce the regulatory initiative for MDs and the importance of a paradigm shift from regulation to innovation regarding MDs.

Medical devices (MDs) range from things like scalpels, needles, x-ray films, digestive catheters, and artificial bones, through to pacemakers and artificial heart valves; software programs can also be included among MDs. MDs can be used by doctors, clinical engineers, nurses, system integrators, system designers, and patients, and the specifications of MDs are often modified and revised during the period of their clinical use. Recent rapid advances in the technology of the Internet of Things now makes it easy to access personal health records and personal clinical data, and artificial intelligence (AI) can process this "big data" and utilize it for medical prognosis, diagnosis, and therapy. These innovative technologies provide new possibilities with the development of MDs with frequently modified behavior in the postapproval phase. For instance, the BRACAnalysis CDx is an MD intended for the qualitative detection and classification of variants in the protein-coding regions and intron/exon boundaries of the *BRCA1* and *BRCA2* genes, aiding in identifying patients with ovarian cancer with the BRCA variants who are most likely to benefit from treatment with olaparib.[1] The classifications of variants may be subjected to change over time as new evidence becomes available for evaluation during the classification process.

Under the current regulatory framework, revision or modification of MDs is classified into either minor or partial changes: with minor changes, notification of the change just needs to be submitted to the regulatory body; with partial changes, an application for change must be submitted to and approved by the regulatory body. The Japanese Ministry of Health, Labour, and Welfare (MHLW) has outlined four criteria that necessitate application for a partial change[2]: when the changes to the MD will increase the foreseeable risks (criterion 1) or produce new risks (criterion 2) for patients; when the influences of the changes on the efficacy and safety of the MD are unclear (criterion 3); and when changes in the structure and principle of the MD can lead to MDs that are different from the parent MD (criterion 4). Under these criteria, most emerging MDs with modifiable behaviors would be subject to constant applications for partial changes because their functions and versions will be continuously changing. Thus, a new regulatory concept is required in order for patients to have timely access to emerging MDs while guaranteeing their safety and efficacy.

It is time for the next revision of the Japanese Act on Securing Quality, Efficacy, and Safety of Products Including Pharmaceuticals and Medical Devices (formerly the Pharmaceutical Affairs Act). A plan for the regulatory framework has been discussed by the Health Sciences Council of the MHLW,[3] a draft version of the Act was proposed to the Japanese National Diet in March 2019,[4] and the revised version of the Act (Act No. 63 of 2019) was published in December 2019.[5] In this paper, we overview an initiative for regulatory control in Japan of emerging MDs that are frequently changeable.

POINTS TO CONSIDER FOR REVIEW OF FREQUENTLY CHANGING MDS, SUCH AS AI ALGORITHMS-DRIVEN

AI can be classified by the type of algorithm used: expert system, machine learning, or deep learning. Expert systems use rules that are created from analysis of data by the users or manufacturers. However, when data sets become too broad and large for the users or manufacturers to make rules, the expert system fails because it cannot create rules from the data by itself. In contrast, machine-learning and deep-learning systems can create rules from the data by themselves. Machine learning is a semi-automatic system because the protocol used to analyze the data needs to be provided by the users or manufacturers. On the other hand, deep learning analyzes data and creates rules by itself. These AI algorithms can continuously modify the behaviors of MDs whenever learning data are input into the MDs.

Since 2005, the MHLW has organized a series of meetings to evaluate novel medical products to allow their timely

[1]Graduate School of Pharmaceutical Sciences, Osaka University, Osaka, Japan; [2]Graduate School of Medicine, Osaka City University, Osaka, Japan. *Correspondence: Masuo Kondoh (masuo@phs.osaka-u.ac.jp)
Received: January 2, 2020; accepted: February 26, 2020. doi:10.1111/cts.12784

access to patients with a guarantee of their safety and efficacy,[6] and, in 2017, a working group was set up to discuss points to be considered for evaluation of algorithms-driven diagnostic MDs in the review by the Pharmaceuticals and Medical Devices Agency of Japan (PMDA). Very recently, draft papers for those points have been published.[7] The characteristics of emerging MDs are unclear because the process between the input of data to the output of data takes place within a "black box." In these cases, the behavior of the algorithms-driven MDs is confirmed by investigating whether the input data lead to the intended output data. For confirmation of their behavior, the marketing authorization holder needs to explain the validity of the input data and the intended output data. Such MDs need to be equipped with an alarm system to notify when unintended behaviors occur, and intended users may be limited to those who can adequately respond to instances of unintended behavior by the MD. If MDs automatically and frequently change in the postapproval phase, there needs to be the capability of managing the MDs remotely by connecting with the marketing authorization holders via the Internet.[7]

It is commonly assumed that MDs will be driven by Internet-connected AI algorithms and, therefore, that the MDs will be able to be managed by the marketing authorization holders. As the specifications of computers improve, however, future MDs will be possibly driven by AI algorithms contained within the MDs themselves. In the latter type of MDs, the behavior of MDs will differ in each clinical situation because the input data will be different in every clinical situation. In these cases, a quality management system for MDs is required. For instance, the marketing authorization holder will provide a standard protocol to users for collection of learning data, quality management of MDs, and confirmation of their behavior. When MDs automatically modify their behaviors in a hospital setting, a hospital clinical engineer should always monitor their operation; system integrators, system designers, and medical device designers also should be responsible for the safe and effective operation of AI algorithms-driven MDs.

A NEW CONCEPTUAL REGULATORY FRAMEWORK FOR FREQUENTLY CHANGING MDS

The Japanese Pharmaceutical Affairs Act is scheduled to be revised within 5 years of it coming into effect in 2014. An MHLW committee discussed revision of the Act in 2018, and discussed a novel regulatory framework for continuously changing MDs. The point is how to balance risk management with timely patient access to innovative MDs. The committee proposed a novel framework wherein plans for partial and minor changes of MDs considered likely to occur in the postapproval phase are confirmed in the initial approval phase.[3]

Under the current review system, the MHLW and PMDA sequentially require appropriate nonclinical and/or clinical data for evaluation of the efficacy and safety of modified MDs. Under the novel review system, the MHLW and PMDA will require both clinical data and a postmarketing partial and minor modification plan when the parent MDs are submitted for application review (**Figure 1**).[8] Once the MDs have been approved, when the modifications are within the scope of the approved postmarketing partial and minor change plan, the MHLW might approve the change application not by review of clinical data but by confirmation of them, resulting in patients having more timely access to the modified MDs than under the current review system with a guarantee of safety and efficacy. This framework is expected to guide appropriate reviews, regulations, and innovations with frequently changing MDs, such as AI algorithms-driven MDs.

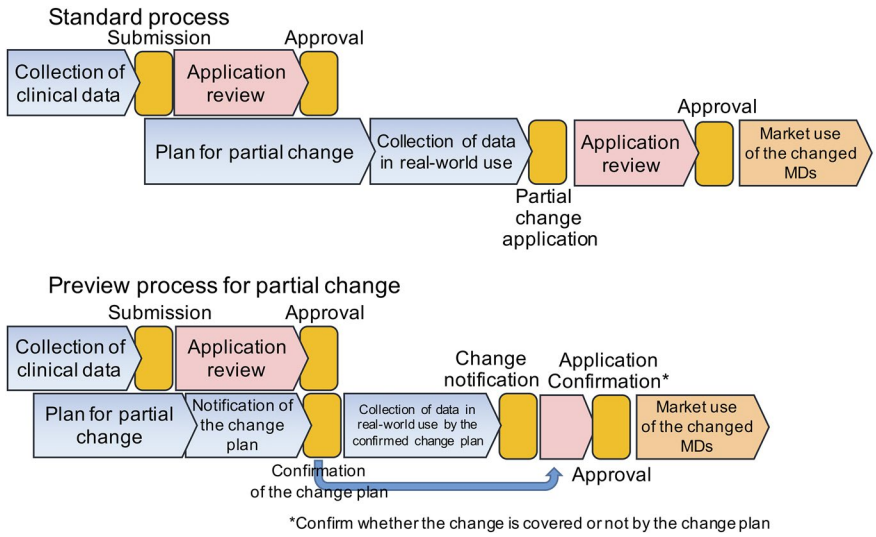

Figure 1 A concept for a regulatory framework to review plans for partial and minor changes in medical devices (MDs). The approval system is to review the clinical data and the postmarketing change plan. When the change occurs in response to collection of data in real-world use according to the approved change plan, it will be confirmed whether the change is within the scope of the change plan. If the change is outside the scope of the plan, the change notification will be rejected.

A PARADIGM SHIFT FROM REGULATION TO INNOVATION

From December 24, 2015, to July 29, 2016, an advisory panel set up by the MHLW discussed how to stimulate innovation for economic growth by Japanese medical ventures, which are venture companies involved with medical devices, drugs, and cellular and tissue-based products.[9] The advisory panel proposed three principles of a paradigm shift in the regulatory framework necessary to spur innovation by medical ventures: from regulation to development, from cautious to speedy, and from macro to micro.[10] The first principle is appropriate regulation from the point of view of the venture company. In this context, this principle does not necessarily mean that regulation is a roadblock to innovation. When regulation is carried out appropriately, it is the actual pathway to achieving real and lasting innovation.[11] That is to say, "Those who master regulation achieve innovation." The second is promotion measured with the sense of urgency of patients, and the third is support suitable for each company. The situation of innovative MDs vs. MDs in general is similar to that of medical venture companies vs. mega pharma because of the smaller scale, larger diversity, and faster speed of development of frequently changing MDs than those of general MDs, such as scalpels, needles, x-ray films, catheters, artificial bones, and pacemakers.[12] A similar paradigm shift also needs to occur with respect to innovative MDs because these innovative MDs require a regulatory framework that promotes their development and their safe access by patients and that these points are optimized for every innovative MD. A series of early approval systems for medical products has already been established in Japan, leading to acceleration of patient access to innovative medical products.[13] The basic concept of that early approval scheme is to balance risks and benefits by rebalancing premarketing and postmarketing burdens considering the characteristics of each medical product. Plans for postmarketing surveillance and criteria for optimal use are reviewed in that conditional early approval system. The concept for the newly proposed regulatory framework for MDs presented in this paper is consistent with this paradigm shift from regulation to development, from cautious to speedy, and from macro to micro.[12]

The behavior of frequently changing MDs is dependent on the quality of data. With regard to this point, the excellent healthcare infrastructure that has been established in Japan gathers health data throughout the whole life of an individual, including even before birth. For instance, under the Maternal and Child Health Act it is obligatory for hospitals to survey the health of mother and fetus during pregnancy by recording data in the maternal handbook and to survey the health of the child from birth until 5 years old. Under the School Health and Safety Act it is obligatory for doctors to survey the health of students in schools, colleges, and universities. Under the Industrial Safety and Health Act it is obligatory to survey the health of employees once a year while people are in the workforce after graduation from school, college, or university. Under the Act on elderly health care, it is obligatory to survey the health of elderly people once they retire from work. Taken together, all people in Japan have personal health records, as defined by the various Acts, for every stage of their lives, even during the fetal stage. The Next-Generation Medical Infrastructure Act, that came into effect on May 11, 2018, will make it possible for academic bodies, government, commercial enterprises, and businesses to use these personal health and medical records for medical research in accordance with procedures determined by the Act.[14] Thus, Japan has the highest quality and the largest quantity of personal health data in the world, and Japan has also established an environment in which personal health records can be utilized for medical innovation. A paradigm shift in the regulatory framework, such as the reviewing of plans for partial and minor changes of MDs at the time of submission for approval, will accelerate development of innovative MDs, such as companion diagnostic devices, leading to cost-effective research and development of drugs in Japan.

Acknowledgments. The authors thank Dr. Kiyohito Nakai and our colleagues for their useful comments and discussions. The views mentioned herein do not necessarily represent the views and findings of the MHLW or the PMDA.

Funding. No funding was received for this work.

Conflict of Interest. The authors declared no competing interests for this work.

1. Summary of safety and effectiveness data of BRACAnalysis CDx. <http://www.pmda.go.jp/medical_devices/2018/M20180420001/750740000_23000BZI00008000_A100_1.pdf>.
2. Notification of partial and minor change of medical devices. <https://www.safetyweb.co.jp/files/medical_equipment/0731_5_h290731.pdf>.
3. A report of the Health Sciences Council in MHLW. <https://www.mhlw.go.jp/stf/newpage_03030.html>.
4. Draft of Japanese pharmaceutical affairs law. <http://www.shugiin.go.jp/internet/itdb_gian.nsf/html/gian/keika/1DCC11E.htm>.
5. The Pharmaceutical and Medical Device Act, Act No. 63 of 2019. <https://www.mhlw.go.jp/content/000489905.pdf>.
6. Regulatory sciences for novel innovative medical products. <http://dmd.nihs.go.jp/jisedai/>.
7. Draft paper for a regulatory framework of artificial intelligence-driven medical devices. <https://search.e-gov.go.jp/servlet/PcmFileDownload?seqNo=0000179718>.
8. A report of the Council on Economic and Fiscal Policy in the Cabinet Office on April, Vol. 10, 2019. <https://www.mhlw.go.jp/content/10807000/000510963.pdf>.
9. Advisory panel for promotion of medical ventures. <https://www.mhlw.go.jp/stf/shingi/other-isei_320773.html>.
10. Summary of report of the advisory panel for promotion of medical ventures. <https://www.mhlw.go.jp/english/dl/20160729.pdf>.
11. Hamburg, M.50 years after thalidomide: why regulation matters. U.S. FDA Blog. <http://www.gmptrainingsystems.com/files/u2/pdf/Hamburg_Why_Regulation_Matters.pdf>.
12. Nakai, K. Regulation for medical device utilizing the artificial intelligence technology in Japan. *Regul. Sci. Med. Prod.* **9**, 17–24 (2019).
13. Matsushita, S. *et al.* A review of the regulatory framework for initiation and acceleration of patient access to innovative medical products in Japan. *Clin. Pharmacol. Ther.* **106**, 508–511 (2019).
14. Act, Next-Generation Medical Infrastructure. <http://elaws.e-gov.go.jp/search/elawsSearch/elaws_search/lsg0500/detail?lawId=429AC0000000028_20180512_000000000000000&openerCode=1>.