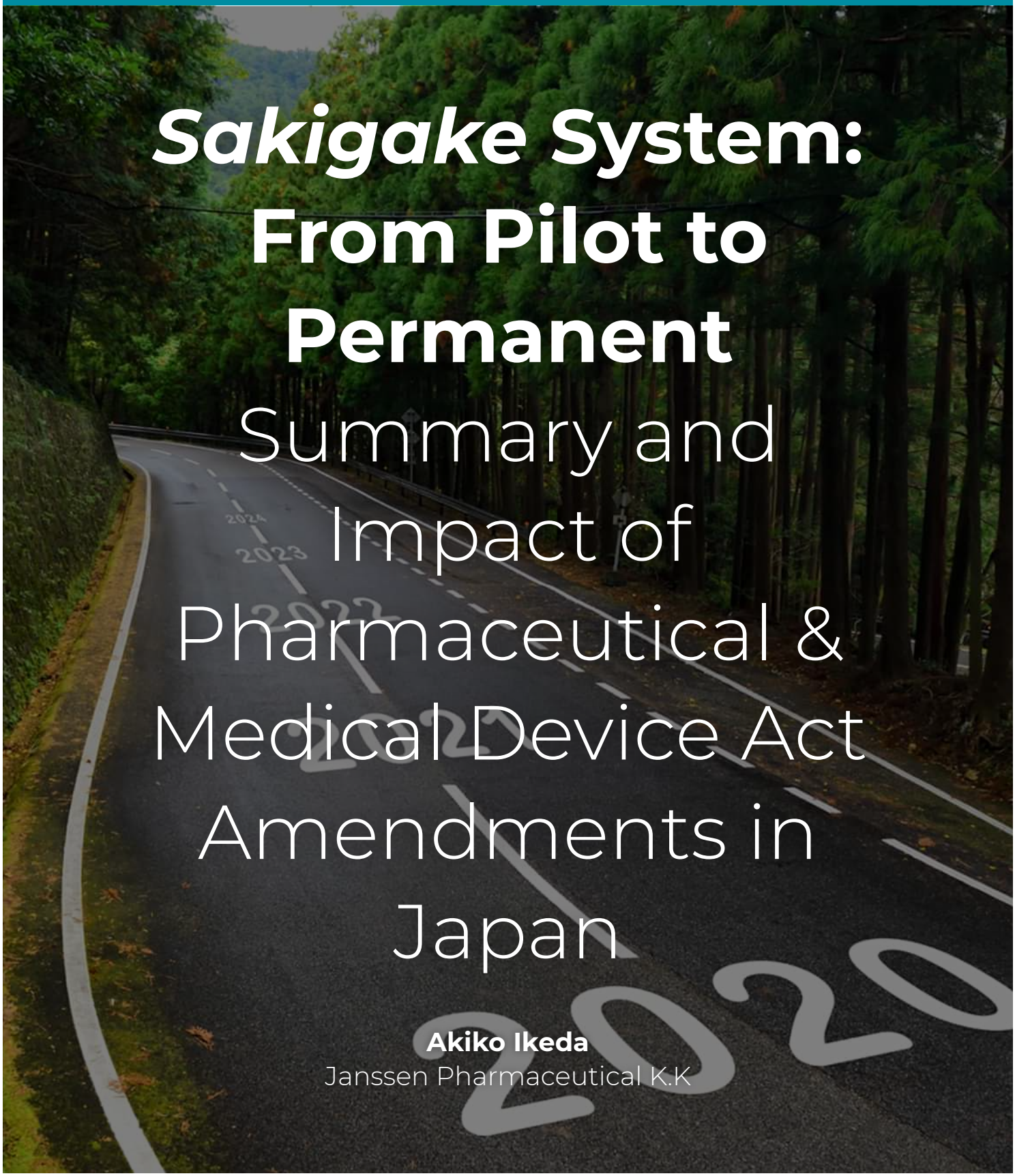

Sakigake System: From Pilot to Permanent

Summary and Impact of Pharmaceutical & Medical Device Act Amendments in Japan

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This summary of the revision of Japan's Pharmaceutical Affairs Act (PMD-Act) issued in December 2019 focuses on two of its three pillars and their impact on companies in Japan. The contents of this revision are broad, they include three pillars and will be implemented by the Government in a stepwise approach over three years:

1. Improvement of systems from development to post-marketing in order to provide pharmaceutical and medical device products safely, quickly, and efficiently.
2. Review of the community roles of pharmacists and pharmacies to improve patient familiarity and peace of mind with using pharmaceutical products.
3. Establishment of regulatory compliance systems to further trust in the healthcare community of Japan.

This article will explore the implementation status and anticipated future impacts of pillars 1 and 3.

Improvement of Systems: Sakigake Designation

The Sakigake designation system of priority consultation, assessment, and review for certain pharmaceutical products has operated as a pilot since April 2015. Its goal has always been to introduce ground-breaking innovations in Japan at the same time as in the rest of the world. This revision of the PMD-Act establishes Sakigake as a permanent system and went into effect on September 1, 2020. The Act allows applicants to seek Sakigake designation at any time; under the pilot system, applicants were allowed to seek this designation only during a narrow window of time (approximately one month) only once a year. It also doubles the designation announcement frequency from once a year (as was the case in the pilot program) to twice a year. This revision also clearly states that a sponsor must submit a Sakigake-designated NDA within 30 days of submitting their first NDA or BLA for the same product in any other country. These provisions make it easier for foreign-affiliated companies to apply for this designation than before.

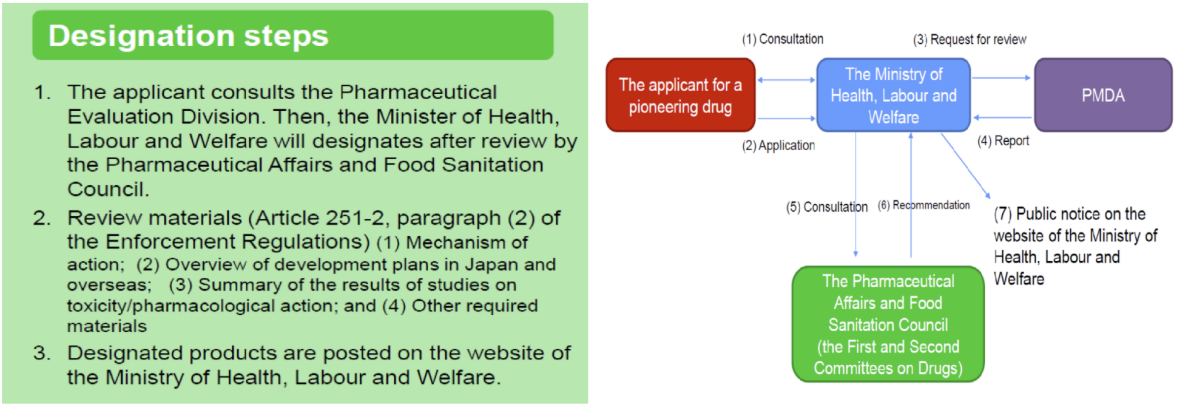

Figure 1. Sakigake designation process per PMD-Act December 2019.

Year	2016	2017	2018	2019	2020
Products Designated	5	5	6	5	3
Products Approved	4	1	3	0	0

Table 1. Comparison of Sakigake product designations versus product approvals.

As the above table shows, there is great room for improvement in implementing Sakigake. Due to resource issues, such as the scarcity of PMDA review officers, the number of Breakthrough Therapy designations under the US FDA and of PRIME designations under the EU EMA will be more than the number of Sakigake designations in Japan for the foreseeable future. This issue of PMDA resources seems to be an ongoing challenge, and may continue to hold back the number of Sakigake designations. As the speed of development of genuinely innovative and groundbreaking new drugs continues to accelerate throughout the world, including and especially Asia, it is critical that Japan continue to refine this Sakigake designation system or else sponsors may choose to conduct clinical trials and to submit marketing applications for these products elsewhere, leaving Japan out. This would be a tremendous disadvantage for and disservice to patients in Japan.

Improvement of Systems: Conditional Early Approval

Since the conditional early approval (CEA) system started as a pilot program in October 2017, four products have been designated and approved (see below).

Product	Indication	Approved
Lorlatinib (LORBRENA)	ALK tyrosine kinase Inhibitor for NSCLC	2018 CEA
Pembrolizumab (KEYTRUDA)	(MSI-High) Solid Cancer	2018 CEA
Viltolarsen (VILTEPSO)	Duchenne muscular dystrophy	2020 Sakigake/ CEA
Cetuximab Sarotalocan Sodium	Unresectable locally advanced / recurrent head and neck cancer	2020 Sakigake/ CEA

Table 2. Products approved under conditional early approval (CEA).

CEA is based upon many of the same factors and conditions as Priority Review, and also enables conditional marketing application approval without requiring the conduct of a confirmatory study.

To alleviate safety concerns in the absence of a confirmatory study, this CEA system features an interim evaluation that allows for early identification and mitigation of safety concerns. As illustrated below, the sponsor commits to submitting interim post-approval safety results according to a specific timeline. Based on these interim results, the sponsor may be directed to change the indication, dose or administration, or precautions in the package insert, for the approved product. This system allows innovative products to quickly reach patients with unmet medical needs and also allows for continued safety evaluation while patients use them. This CEA pilot program was made permanent effective September 1, 2020.

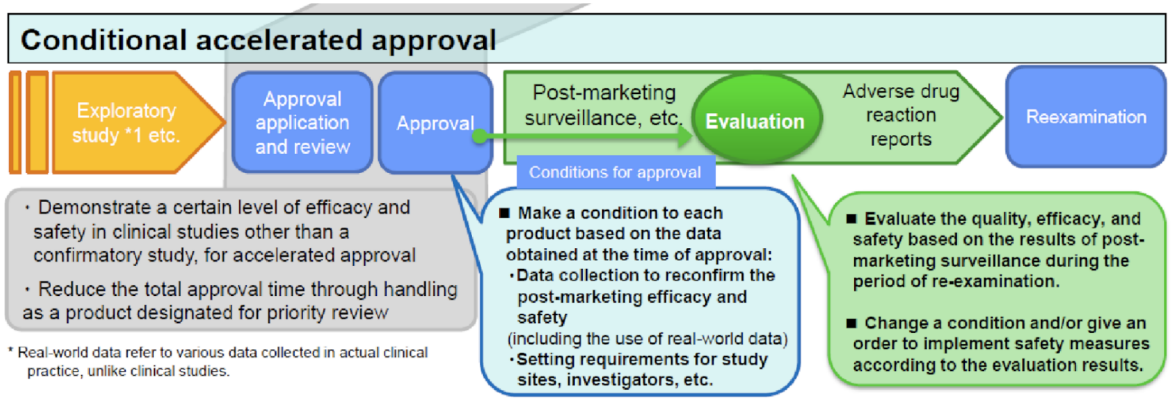

Figure 2. Conditional accelerated approval flowchart.

Improvement of Systems: System for Drugs for Specific Use

The Drug for Specific use is a new category established by the PMD-Act and came into effect on September 1, 2020. This system is designed to avoid off-label use, to ensure proper use of these products by clinical investigators and research institutions, and to get approval for

these additional indications, especially in areas of antimicrobial drug resistance (AMR) and high unmet pediatric patient needs. Designations are discussed and granted through the MHLW Review Committee for products for unmet medical needs.

Furthering Trust: Clinical Trial Notification and Safety Reporting in Clinical Development

This revision of the PMD-Act also changed the drugs for which adverse reaction reports are required from the "study drug"* to "all drugs in the clinical trial"** *(Please see figures below.)* Before this revision, sponsors and investigators were required to report adverse reactions from only the principal component (study drug) involved in clinical trials. This amendment expanded the scope to include all drugs used in the protocol (including concomitant drugs, study drugs, and rescue drugs) and expanded the obligation to report adverse reactions to the sponsor. This revision also implemented a change to the clinical trial notification system to handle more complex trials and these additional safety reports. The two-year transitional period of switching to this new regulation began on September 1, 2020, toward the target date of September 1, 2022.

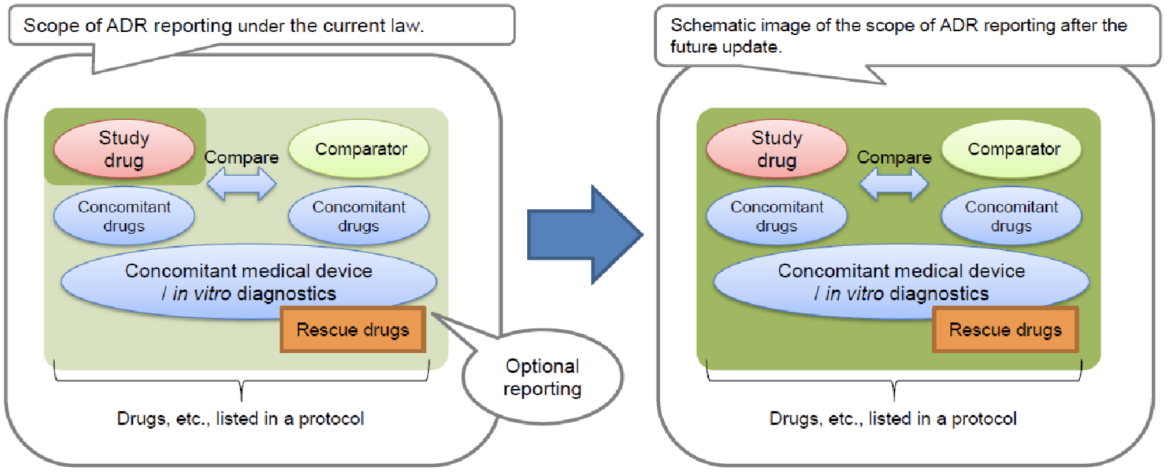

Figure 3. Comparison of present and future states of ADR reporting.

*Study Drug is the main compound being studied in the clinical trial.
**All Drugs means not only the main compound being studied but also concomitant drugs, rescue drugs, or other approved drugs mentioned in the study protocol.

Looking Forward

Many of these changes have been or will be being implemented in a stepwise approach. Changes have either recently come into effect (September 2020) or will come into effect by 2022.

We must now enter a period of collecting, analyzing, and understanding the results of these changes to identify their impact on industry, health authorities, regulatory bodies, and patients in Japan, and to determine our best next steps for the future implementation stages.

All figures based on an October 22, 2020, briefing by the Federation of the Pharmaceutical Manufacturers' Associations of Japan (FPMAJ).