Asia Pacific *Japan*

Balancing safety and efficiency: updating the regulation on pharmaceuticals and medical devices

It's been five years since both the name and the content of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (the "Act")[1] were changed in 2014. Now the government's once again planning to update this primary source of regulation for pharmaceuticals, cosmetics, medical devices and utensils. On 25 December 2018, a committee (the "Committee") appointed by the Ministry of Health, Labour and Welfare (the "MHLW") issued an opinion setting out the principles and framework of the amendment to the Act.[2] The Cabinet submitted the draft amendment to the Act to parliament on 19 March 2019 (the "Amendment"), aiming to have it passed during 2019.

The Amendment covers various aspects of the pharmaceutical industry. Most significantly, it contemplates achieving a) rapid access to innovative pharmaceuticals and medical devices and b) tighter governance of manufacturing, distribution and sales enforced through administrative surcharges. The focus is on creating a system where beneficial pharmaceuticals and medical devices can be rapidly developed for use in Japan (ie minimising time-lag in drug and device development). The Regulation's aim is also to ensure safety by introducing a more efficient quality management system with advanced technology and data collected in a regulated manner.

Rapid Access To Innovation

New pharmaceuticals must be approved by the Pharmaceutical and Medical Devices Agency (the "PMDA") before being launched on the market; ordinary screenings take around 11.8 months, with priority screenings taking approximately 8.3 months (in approximately 80% of cases in 2018).[3] The median of the screening period for new active substances ("NAS") was 333 days in 2018.[4] Although this isn't a bad score, the PMDA wants to find ways to expedite the process for advanced medicines. To this end, the Amendment will formally enact and add clearer conditions for the temporary schemes included in the SAKIGAKE Designation System (launched in 2015[5]) and the Conditional Rapid Authorization System (launched in 2017[6]).

The SAKIGAKE Designation System includes prioritisation in the consultation and review process. It was introduced to ensure early practical application of innovative pharmaceuticals and medical devices by encouraging R&D and early clinical research/trials in Japan[7] (reducing the screening period by up to six months).

The Conditional Rapid Authorization System allows for acceleration of the practical application of unapproved/off-label drugs[8] (especially orphan drugs) for serious but rare diseases. It enables Phase III clinical trials to take place before practical application,[9] subject to certain conditions. These include limiting facilities where a product can be administered and requiring post-approval test and report of safety and efficacy on a continuous basis. It allows for the use of real-world data ("RWD") in certain circumstances, especially where the number of targeted patients is significantly small.

For medical devices, the Committee has issued an opinion on improving the Innovative Medical Devices Conditional Rapid Authorization System. It enables authorization to be extended quickly to a) use of devices for other parts of the body, and b) any improvements made after the manufacture and sale of the devices in accordance with approved improvement plans.

1 Act No. 145 of 1960 as amended

2 Opinion on the amendment of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (in Japanese) https://www.mhlw.go.jp/content/11121000/000463479.pdf

3 Achievement of the Operation in 2018 and Future Actions (PMDA, December 2018) https://www.pmda.go.jp/files/000227251.pdf

4 Ibid

5 Under the SAKEGAKE Designation System, five pharmaceuticals were designated in 2015, five in 2017 and six in 2018; one medical device was designated in 2016, three in 2017 and two in 2018.

6 Under the Conditional Rapid Authorization System, two pharmaceuticals were designated in 2018.

7 To qualify for the SAKIGAKE Designation System, the pharmaceutical must be: i) an unprecedented invention; ii) targeted at a serious disease; iii) significantly effective against the target disease; and iv) applied for clinical use in Japan and/or worldwide.

8 Strategy of SAKIGAKE by the Ministry of Health, Labor and Welfare https://www.mhlw.go.jp/english/policy/health-medical/pharmaceuticals/140729-01.html

9 To qualify for the Conditional Rapid Authorization System: i) the target disease must be serious (ie life-threatening, with an irreversible and substantial impact on the daily life of the patient, or other reasons); ii) the pharmaceutical or medical device is highly effective to the target disease because there is no existing medication or the pharmaceutical or medical device is more favourable than existing medication; iii) phase III clinical trial is difficult or takes extensive period of time due to the small number of patients etc.; and iv) the pharmaceutical or medical device has been proven to be effective and safe to a certain level by clinical trials or other methods other than phase III clinical trial.

The Committee also indicated tightened regulation of clinical trials, improved traceability, and globally-harmonised quality management methods. This will include revising reviews of conformity with "Good Manufacturing Practice" ("GMP") and "Good Gene, Cellular and Tissue-based Products Manufacturing Practice" ("GCTP") on a facility, instead of a manufacturer, basis. It also includes relaxing requirements for reviews of the "Quality Management System" ("QMS"), and risk-based approaches to changes in approvals.

Introducing Tighter Governance

The Committees made various suggestions for introducing tighter governance of manufacturing, distribution and sales. These include enforcing a barcode system, improving the traceability of pharmaceuticals and medical devices through the supply chain, and tightening the approval system for authorised manufacturers and sellers of products. The most significant suggestion of all is for the introduction of administrative surcharges on false or misleading advertisements, and sales of unapproved pharmaceuticals. While these are already prohibited under the Act, the scope of criminal liability is narrow and fines are relatively low (maximum JPY 2 million for an individual and JPY 100 million for a company) – unlikely to deter future violations when some blockbusters can bring in many billions of dollars in revenues.[10] This was raised following recent scandals where several companies delayed reporting side effects, manipulated clinical data, and manufactured certain pharmaceuticals without authorisation. The surcharge will be calculated as up to 4.5% of revenues from pharmaceuticals or medical devices sold as a result of unlawful advertising or acts.

Comment

Many stakeholders have been waiting for this update of the Act. And although it's challenging to achieve a balance between speedy procedure and safety protection, the Amendment will definitely bring more foreseeability to the process and create a more favourable environment for effective clinical development, manufacturing and distribution of pharmaceuticals and medical devices in Japan.

Tighter governance of the end-to-end supply chain for pharmaceuticals and medical devices will help ensure integrity and compliance in the industry. This will benefit not just patients but all market participants, including doctors, researchers and pharmaceutical companies. At this point, it's not certain whether the Amendment will be passed by parliament this year. But as the Committee has said, and regardless of the Act, all parties need to think about how they can improve the quality, effectiveness and safety of pharmaceuticals and medical devices.

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10 Although the Act also provides a penalty of imprisonment of up to 2 years for a case of misleading or false advertisement, Japanese prosecutors are cautious about bringing criminal charges for this kind of crime under a concern for balancing crimes with appropriate punishments. In addition, ethical violations at the development stage or in the communication not amounting to a prohibited false "advertisement" are not effectively regulated.