

## Japan as a case study of national “readiness” for regenerative medicine

Regenerative medicine (RM) involves the therapeutic application of cells, tissues and genes to repair or regenerate damage to the human body that has occurred as a result of disease or injury. The idea of “regenerative readiness” holds that, as well as developing new cell- and gene-based medicines, it is also necessary to improve institutional capacities and implement suitable infrastructure, training, and regulation, to make routine use of regenerative medicines in healthcare a viable prospect. [1] Much of the work of creating a suitable economic, regulatory and skills-based environment for regenerative medicines takes place at the national level. This article focuses on Japan, as a country with a strong and distinctive strategy for delivering RM, and outlines Japan’s efforts to build regenerative readiness. .

Japan has engaged in a national, system-wide effort to build regenerative readiness. This takes the form of an “All Japan” collaboration between government, industry and academia to develop an ecosystem to make regenerative medicine viable. Japan has a long history of medical innovation, with robust state support for cell therapy since at least the year 2000. This initially took the form of funding for medical research and the production of new regulatory guidelines for trialling cell therapies in clinical practice. Much of the recent effort has been propelled by the exuberance surrounding the discovery, and subsequent Nobel Award, for a novel type of stem cells, known as ‘induced pluripotent stem cells’, by Japanese scientists at the University of Kyoto. Hopes to capitalise on this technology of Japanese origin, and build a globally competitive industry, led to a range of initiatives across government, industry and academia to build a supportive ecosystem and advance system-wide readiness. [2]

As a highly regulated field, readiness efforts are perhaps most readily visible in government initiatives to facilitate industrial development and clinical delivery of RM. To this end, two new laws governing regenerative medicines were introduced in 2014: the Pharmaceuticals, Medical Devices and Other Therapeutic Products Act (PMD Act) and the Act on the Safety of Regenerative (ASRM).

The PMA Act is the more conventional of the two laws. It is essentially an updating of the existing Pharmaceutical Affairs Law, to make explicit provision for RM products being developed by industrial producers for market access. This is similar to current regulatory pathways for RM medicinal products in the EU and USA, although the PMD Act does make special provision that allows regenerative therapies to be offered to certain patients on a for-profit basis before they have secured full regulatory approval. This 'conditional approval' of regenerative therapies can be applied for after phase 2 clinical trials, if safety and efficacy are adequately predicted by existing trial data. The products are then required to establish safety and efficacy within a designated time, up to a maximum of 7 years, after which their marketing approval can either be further extended or withdrawn.

The ASRM is more unusual in that it provides a second, parallel regulatory pathway for both research and clinical use of RM therapies in hospital settings. Clinical research covered by the ASRM is considered distinct from clinical trials run by companies, which are regulated under the PMD Act. This law was intended to bring private provision of unapproved cell and tissue based products under control, while at the same time providing a structured framework to support clinical innovation as a valid way to develop new treatments in Japan. [3]

These regulatory adaptations were not made in a vacuum. The Japanese Society for Regenerative Medicine (JSRM) was highly instrumental in encouraging regulatory change, partly for Japanese scientists, who argued that the prevailing regulatory framework should be revised to accommodate the new technological modality. The JSRM is rather unique as an academic association in that has many industry members, and has also historically lobbied for government reforms in support of industry interests.

Industry has also been an integral part of building readiness in Japan. Developing industrial mass production capacity, thereby standardising the quality and

lowering the prices of regenerative medicines, has long been considered important to the delivery and widespread adoption of RM therapies among a large population. The impetus for industrialisation also been helped by the aforementioned desire to capitalise on a technology of national origin and develop a globally competitive industry.

As the membership of the Japanese industry association, FIRM, reflects, industry efforts to build the regenerative field are characterised by a cross-sector effort to build an eco-system. FIRM membership ranges from logistics providers to insurance companies, and therapy developers. In addition to smaller start-ups working on cell or gene therapies, larger established firms from a range of sectors have entered the regenerative medicine field in Japan. These include Fujifilm, J-TEC (from medical device maker Nidek), and Terumo (another medical device company). [4]

This network building aspect is also seen in the work of the JSRM. The society is engaged in a range of readiness activities, such as “match-making” activities between academia and industry, engaging with patient organisations, and hosting public lectures to increase awareness of regenerative medicine. Indeed, recognising the importance of education and need to develop human capital [5], JSRM has established a training and certification programme for cell cultivation technicians, published a regenerative medicine textbook targeted to all stakeholders involved in the field of regenerative medicine across the value chain.

Recent efforts by JSRM to promote readiness also include a national consortium to support clinical research and delivery of regenerative medicine, sponsored by AMED, Japan’s national medical research funding agency. The consortium includes activities beyond the clinical setting, such as education, considering regulatory adjustments, and developing a national registry. The latter, referred to as the *National Regenerative Medicine Database*, records data from ongoing clinical research and post-marketing surveillance studies of regenerative therapies.

Readiness is context dependent [1], so some of the initiatives described will only make sense in the context of the existing Japanese regulatory and healthcare system. However, other readiness initiatives may act as a useful example for further countries to follow. In particular, clinical – physician-led – innovation is typically limited to surgical procedures, care provision pathways, and one off ‘compassionate use’ interventions in much of the rest of the world, so it will be instructive to monitor whether the ASRM leads to a swathe of new regenerative treatment options in Japan.

## References

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