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Japan's Conditional Approval Pathway for Regenerative Medicines

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This article discusses the history, reasoning, legal decisions and subsequent regulatory requirements behind Japan's bid to become a world leader in regenerative medicine. The authors outline the process for seeking new regenerative product approvals through an accelerated regulatory pathway and spell out the oversight role played by Japan's regulatory authorities to enable new regenerative, cell-based therapies to be made available to the public in Japan as soon as possible, but with assurances of safety and efficacy.

Introduction

In 2006, researchers at Japan's Kyoto University found a way to genetically reprogram specialized adult cells to act like embryonic stem cells. These engineered cells, called induced Pluripotent Stem Cells (iPSCs), can be used in various stem cell therapies, but without the ethical problems posed by harvesting embryonic stem cells for therapeutic use. The initiative for developing a conditional approval pathway for regenerative medicines in Japan was inspired by the award of the 2012 Nobel Prize in Physiology and Medicine to Shinya Yamanaka of Kyoto University for his work on iPSCs.[1]

On 26 April 2013, the Japanese Diet passed the *Regenerative Medicine Promotion Law*.[2] This new law reflected a sentiment that the Japanese government had a responsibility to make regenerative treatments available to its citizens. The new law called for the development of policies to promote research and establish regulations supporting regenerative medicine technologies.

The *Regenerative Medicine Promotion Law* amended the *Pharmaceutical Affairs Law*, which was renamed the *Pharmaceuticals, Medical Devices, and other Therapeutic Products Act* (*PMD Act*) and passed 27 November 2013. It became active 25 November 2014. Along with this

revision, a new act, *the Act on the Safety of Regenerative Medicine*, was also passed and became active at the same time.[3]

Another driving force for the new legislation was the recognition that the existing framework in the pharmaceutical affairs law was not consistent with the heterogeneous characteristics of regenerative medicine products, including cellular therapies, gene therapies and accompanying devices. Thus, the outcome of amending the *Pharmaceutical Affairs Act* to the *PMD Act* encouraged cutting-edge research in regenerative medicine to enable conditional approval pathways for regenerative medicines and devices. It also aimed at securing Japan's global leadership role in regenerative medicine technology.

Toward the Prompt and Safe Provision of Regenerative Medicine

Regenerative medicine products are a distinct class, separate from pharmaceuticals and medical devices. Regenerative medical products are intended to be used for the reconstruction, repair or formation of structures or functions of the body (e.g., tissue-engineered products) or for the treatment or prevention of diseases (e.g., cell therapies). Gene therapies, defined as those intended for use in the treatment of disease and transgened to be expressed in cells, are also considered regenerative medical products.[4]

Under the new framework, clinical studies for regenerative medicine products are approved through the Clinical Trial Notification (CTN) system, as are pharmaceuticals and medical devices. Consultations, required for regenerative medicine products prior to submission of a CTN, are also managed in a similar fashion as those for pharmaceutical products and medical devices, although the consultation may be more detailed for regenerative medicine products.

It is possible for regenerative medicine products comprised of heterogeneous components to receive conditional approval with a limited clinical data set, as long as the data demonstrate a safety profile of the new product consistent with the severity of the disease or condition being treated along with efficacy data predicting probable patient benefit. Probable patient benefit may be demonstrated with data sets from exploratory clinical trials and may be based on predictive surrogate endpoints.

In practice, a conditional approval with a limited data set will be granted after consultation with the *PMDA* to discuss the design of the trial and the data set to be considered for getting conditional approval. More than one consultation from early stages of development will likely be needed to achieve agreement on the study design.

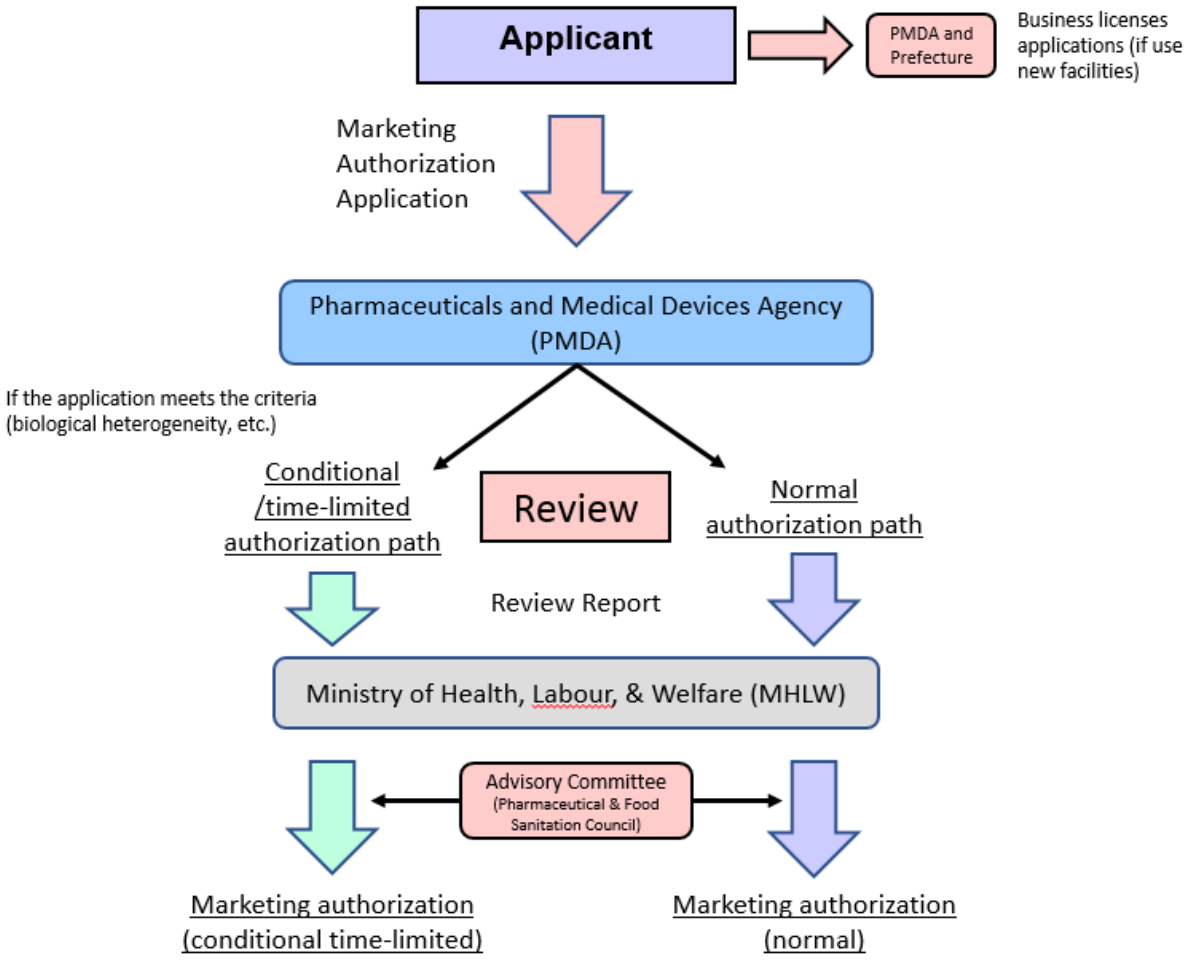
Once data generation is complete, a Japan New Drug Application (JNDA) is prepared and submitted and subjected to a review process similar a review for pharmaceutical products (**Figure 1**).[5] The JNDA is first reviewed by the PMDA and a report is written which may recommend for or against approval of the product. The report may set out conditions for

approval. The report is then submitted to the MHLW for consideration. An advisory committee may be engaged to assist MHLW in its deliberations.

A conditional approval will be time-bounded and include requirements for further studying the safety and efficacy of the regenerative medical product during the conditional approval period. The conditional approval period may be as long as seven years or fewer, as determined at the discretion of the Japanese regulators. At the end of the conditional approval period, a re-application must be submitted to continue marketing the regenerative medical product and the PMDA/MHLW review and decision process will be repeated. The regenerative medical product's marketing authorization may be revoked if the safety and efficacy of the product has not been corroborated.

An additional requirement may be imposed to restrict the regenerative medical product's use to only those physicians or institutions with special knowledge about—or training in—the use of the product.

Figure 1[6]



In order to assure the safety of conditionally approved regenerative medicine products, three additional conditions are required by regulation. First, each patient receiving a regenerative medicine product must be informed of its conditional approval status and the expected risks and benefits before the patient consents to the treatment. Second, post-marketing surveillance must be conducted and regular reports on the safety of the regenerative medicine product must be submitted. Finally, if a patient's health is damaged due to the regenerative medicine product, the patient may be compensated by Japan's Relief Services for Adverse Health Effects.[7]

Guidance Documents, Notifications and Ordinances

Japanese regulators have produced a large number of relevant guidance documents to assist developers of regenerative medicine products. Many were issued before the *PMD Act* was revised, but specific guidances related to the new *PMD Act* also have been issued (**Table 1**). Only a small number of these are officially translated into English by Japanese regulators and there is no central source for obtaining translations.

Table 1. Selected Regulations and Guidance Documents Related to Regenerative Medicine Products[8,9]

Title	Reference
Ordinance on good gene, cellular and tissue-based products manufacturing practice	Ministerial Ordinance No. 93 (6 August 2014)
Regulations for Buildings and Facilities for Pharmacies, Good Gene, Cellular and Tissue-based Products Manufacturing Practice (GCTP) and Good Quality Practice (GQP) for regenerative medical products	Pharmaceutical and Food Safety Bureau Director Notice 0812 No. 11 (12 August 2014)
Good gene, cellular and tissue-based products manufacturing practice	Compliance Division Director Notice 1009 No. 4 (9 October 2014)
Guidance on designation of biological products and regenerative medicine products	Evaluation and Licensing Division Director Notice 1105 No. 1 (5 November 2014)

Table 1. Selected Regulations and Guidance Documents Related to Regenerative Medicine Products[8,9]

Title	Reference
Guidance on designation of biological products and regenerative medicine products	Medical Device and Regenerative Medicine Product Evaluation Division Director Notice 1105 No. 2 (5 November 2014)
Guidelines for assurance of quality and safety of drugs and medical devices processed from cells and tissues of human origin	Pharmaceutical and Medical Safety Bureau Director Notice No. 1314 (26 December 2000)
Guidelines on ensuring quality and safety of autologous human cell/tissue-based products	Pharmaceutical and Food Safety Bureau Director Notice 0208 003 (8 February 2008)
Guidelines on ensuring quality and safety of allogeneic human cell/tissue based products	Pharmaceutical and Food Safety Bureau Director Notice 0912 006 (12 September 2008)
Guideline on ensuring quality and safety of products derived from processing: human embryonic stem cells	Pharmaceutical and Food Safety Bureau Notification No. 0907-6 (7 September 2012)
Guideline on ensuring quality and safety of products derived from processing: human autologous somatic stem cells	Pharmaceutical and Food Safety Bureau Notification No. 0907-2 (7 September 2012)
Allogeneic human somatic stem cells	Pharmaceutical and Food Safety Bureau Director Notice 0907 No. 3 (7 September 2012)

Table 1. Selected Regulations and Guidance Documents Related to Regenerative Medicine Products[8,9]

Title	Reference
Autologous human induced pluripotent stem-like cells	Pharmaceutical and Food Safety Bureau Director Notice 0907 No. 4 (7 September 2012)
Allogeneic human induced pluripotent stem-like cells	Pharmaceutical and Food Safety Bureau Director Notice 0907 No. 5 (7 September 2012)
Guideline on ensuring the quality and safety of products derived from processed human stem cells	Pharmaceutical and Food Safety Bureau Director Notice 0907 No. 6 (7 September 2012)
Notes on reporting defects in clinical trials related to processed cells	Pharmaceutical and Food Safety Bureau Notification 1002-1 (2 October 2014)
Enforcement regulations included provisions for reporting criteria and deadline of malfunction reports of regenerative medicine products	Pharmaceutical and Food Safety Bureau Notification 1002-20 (2 October 2014)
About handling defect reports on clinical trials related to processed cells	Medical Device Trial Instruction No. 1107004 (7 November 2014)
About partial revision of handling defect reports on processed cells	Medical Device Trial Instruction No. 0318001 (18 March 2016)

Table 1. Selected Regulations and Guidance Documents Related to Regenerative Medicine Products[8,9]

Title	Reference
Guideline for assuring the quality and safety of gene therapy products	Ministry of Health, Labor, and Welfare Pharmaceutical Affairs Bureau Notification No. 1062 (15 November 1995)
	Revision 1 (29 March 2002)
	Revision 2 (28 December 2004)
Guidelines of quality and safety assurance of drugs for gene therapy	Pharmaceutical and Food Safety Bureau Evaluation and Licensing Division Notification No. 0701-4 (1 July 2013)
Reporting of information and findings that may affect the evaluation of drugs for gene therapy	Pharmaceutical and Food Safety Bureau Evaluation and Licensing Division Notification No. 0701-7 (1 July 2013)
Regarding the enforcement of ministerial ordinance to amend part of the enforcement regulations of the Pharmaceutical Affairs Law (about handling of cellular tissue drugs and cellular tissue medical devices)	Notification No. 266 (28 March 2001)
Points to consider on manufacturing and quality control of autologous human cellular and tissue-based products	Notification No. 0327025 (27 March 2008)

Table 1. Selected Regulations and Guidance Documents Related to Regenerative Medicine Products[8,9]

Title	Reference
Guidelines on clinical research using human stem cells	Ministry of Health, Labor, and Welfare (3 July 2006 and amended 1 November 2010)
Regarding the enforcement of ministerial ordinance concerning standards of safety management after manufacturing and sales of pharmaceuticals, quasi-drugs, cosmetics, medical equipment and regenerative medical products	Pharmaceutical and Food Safety Bureau Notification No. 0812-4 (12 August 2014)
Clinical trials notification for clinical trials related to processed cells	Pharmaceutical and Food Safety Bureau Notification No. 0812-26 (12 August 2014)
Safety reporting for regenerative medicines	Pharmaceutical and Food Safety Bureau Notification No. 1002-23 (2 October 2014)
Guidance on nonclinical safety for regenerative medicine products	Ministry of Health, Labor, and Welfare (8 March 2013)
Guidance on quality of regenerative medicine products	Ministry of Health, Labor, and Welfare (8 March 2013)
Current Perspective on Evaluation of Tumorigenicity of Cellular and Tissue-based Products Derived from induced Pluripotent Stem Cells (iPSCs) and iPSCs as Their Starting Materials	Ministry of Health, Labor, and Welfare (21 August 2013)
Guidance on sterility and mycoplasma tests for regenerative medicine products	Ministry of Health, Labor, and Welfare (17 January 2014)
Trial implementation of pioneering designation system for medical devices In vitro diagnostic drugs Regenerative medicine etc. (Third)	Department of Medical Inspection Notification 1005-1 (5 October 2017)

Table 1. Selected Regulations and Guidance Documents Related to Regenerative Medicine Products[8,9]

Title	Reference
Ordinance for standards for conducting post-marketing surveys and studies on regenerative medicine products	Ministry of Health, Labor, and Welfare Ordinance No. 90 (30 July 2014)
Description methods of basic plan for evaluation of post-marketing approval conditions and basic plan of post-marketing surveys for regenerative medicine products	Pharmaceutical and Food Safety Bureau Notification No. 0826-1 (26 August 2015)

SAKIGAKE Designation

The Japanese regulatory authorities have developed an accelerated pathway for innovative pharmaceuticals, medical devices, *in vitro* diagnostics and regenerative medicine products using the best concepts from accelerated pathways employed in other regions. The result was the SAKIGAKE designation,[10,11] introduced in Japan in 2015. It is similar in concept to breakthrough designation in the US or PRIME designation in Europe.[12]

The criteria for SAKIGAKE designation are:

- Innovative product for a disease in dire need of innovative therapy; can include new indications, new target diseases, new drug delivery systems which are expected to greatly improve the efficacy.
- Prominent effectiveness (i.e., radical improvement compared to existing therapy) can be expected based on the mechanism of action from non-clinical study and early phase clinical trials.
- Intended to treat a serious disease with significant impact on life or a disease with chronic debilitating conditions.
- Addresses an unmet medical need for the target disease.
- There is no approved drug(s) for the condition or the new product contributing to a significant improvement of efficacy/safety compared to drug(s) already approved for the condition.
- There is intent for the product to be introduced in the Japanese market first or at least in parallel with release in other markets. It is to be a therapeutic agent for which domestic development is progressing steadily or an agent fulfilling either or both of the following conditions:
    - First-in-human (FIH) study was conducted in Japan.

- Proof of Concept (POC) study was conducted in Japan.

These criteria are similar to those in the US and Europe, but with a major difference. The award of a SAKIGAKE designation requires an emphasis on developing the new product first in Japan or at least not later than in other regions. This fulfills one of the driving forces of advanced regenerative therapy legislation in Japan making these technologies available to patients in Japan first and to keep Japan a leader in regenerative therapy technologies.

Among the benefits of SAKIGAKE designation are:

- prioritized consultation with PMDA under a system in which a "concierge" is assigned and is responsible for helping the sponsor expedite the product through the Japanese regulatory system
- substantial pre-application consultation to ensure submissions are high quality
- priority review of pre-market applications
- extension of the re-examination period once an approval is granted
- potential for premium pricing for the new product

Pricing concessions are a substantial benefit to SAKIGAKE designation and are not part of conditional approval schemes in other regions.

Requirements for submitting a SAKIGAKE designation request are designed to be efficient. Specific forms and instructions are provided in a notification by the MHLW.[13] The forms are slightly different depending on whether the product is a medical device, an *in vitro* diagnostic or a regenerative medicine product. For example, for a regenerative medicine product, Form 1-3, limited to one page, collects information about the sponsor and the product and calls for justifications that the product is innovative and addresses an unmet medical need for a life threatening, serious disease (**Table 2**). It is also necessary to provide justification of clinical evidence regarding the effectiveness of the product and also to confirm the product will be developed in Japan ahead of the rest of the world. Preferred dates for a hearing with the PMDA are also provided along with contact information. There is an attachment in which further detail can be provided for each of the requirements (**Table 3**).

Table 2. Application for SAKIGAKE Designation for a Regenerative Medicine Product (Form 1-3)[14]

Applicant's name		
Approval number		
Name	General name	
	Trade name	
Scheduled efficacy, effect or performance		
Shape, structure, ingredient, quantity or essence		
Scheduled usage and dosage or use method		
Mechanism of action		
Applicability to specified requirements		
Requirement 1	Treatment's innovation	
Requirement 2	Seriousness of the target disease	
Requirement 3	Prominent effectiveness on target disease	
Requirement 4	Willingness/framework for early development and application in Japan ahead of the world	
Preferred Hearing Date	First choice	
	Second choice	
	Third choice	
	Fourth choice	
	Fifth choice	
	Sixth choice	
Person in Charge Contact Information	Name	
	Deployment name	
	Telephone number	
	Fax	
	E-mail	
Remarks		

Table 3. Information Attachment for SAKIGAKE Designation for a Regenerative Medicine Product[15]

Applicant's name		
Name	Generic name	
	Trade name	
Requirement 1	Treatment's innovation	□ Novel mechanism of action □ Other (specify)
	(Summarize why you believe it meets this requirement)	
Requirement 2	Seriousness of the target disease	□ Serious illness with significant impact on life □ Diseases in which radical therapy is absent and symptoms (conditions in which social life is difficult) continue
	(Outline of target disease)	
Requirement 3	Extremely relevant to the target disease High effectiveness	□ There is no existing treatment □ Significant improvement in efficacy is expected compared to existing treatments
	(Current treatment modalities of subject diseases, summary of test results, etc. suggesting effectiveness)	
Requirement 4	Willingness / structure to early development and application in Japan ahead of the world	□ It is planned to apply for approval in Japan (alone) in the world ahead □ Japan will be included as a target for conducting approval applications for the first time in the world (only when targeting multiple countries/areas) □ I have a system that can apply for approval
	Approval application schedule timing	
	(Progress on development – schedule overview)	

Japan limits the number of SAKIGAKE designations awarded each year. Too, there are strict deadlines for SAKIGAKE applications. The application system is evolving, but so far these deadlines have occurred about once per year, but the deadlines can be different for

pharmaceuticals versus medical devices, regenerative medicine products and *in vitro* diagnostics. Deadlines are announced via formal notifications. For example, the third round for designation requests for medical devices, diagnostics and regenerative medicine products was made on 5 October 2017 with a submission deadline of 22 November 2017.[16] The designated products were announced on 27 March 2018.[17]

Their evaluation follows a four-step process:[18]

1. Public offering for a round of designations; usually about one month is allowed for applicants to submit the designation requests
2. Hearings and preliminary screening. Each applicant has a hearing with PMDA's SAKIGAKE staff who screen the applicants for further consideration.
3. Entries passing the initial screening are further evaluated and prioritized.
4. Designations are selected and reports prepared for each product to be designated. This step includes preparation of material that will be released to the public. A press release will be issued by PMDA.

Once a SAKIGAKE designation is awarded, PMDA will assign a concierge, who will organize a preliminary meeting and work with the sponsor to interface with PMDA departments as necessary and to help the sponsor negotiate a pathway to approval in an expedited and efficient fashion.

Speed and Efficiency

The concept behind the conditional approval pathway is that a product can be approved based on data confirming safety and predict efficacy and the pivotal confirmatory trial(s) are allowed to occur after the product is marketed and made available to patients in Japan. This is shown graphically in **Figure 2**. Via the conventional approach, one or more pivotal registration studies were needed before making an application for marketing authorization. In the new approach, a conditional marketing authorization may be granted based on a single, small-scale trial. Once more, the sponsor can market the product while performing one or more confirmatory studies. The duration of time between initial conditional approval and re-application can be as long as seven years, although this period may be shorter as determined by Japanese regulators.

Since the implementation of the new conditional approval pathway, three regenerative medicine products have been approved in Japan (**Table 4**). Of these three, HeartSheet® was given a conditional approval for heart failure due to ischemia.[19] In this case, two conditions were imposed. The first required Terumo to ensure the product would only be used for its intended purpose and according to its approved label. The second requirement was to conduct a post-marketing evaluation in all patients transplanted with the product during the

conditional approval period. The duration of the approval was set at five years with a re-approval with additional data required after that period to continue marketing the product.

The primary data set for conditional approval of HeartSheet® was from a Japanese clinical trial in which seven patients with severe heart failure due to ischemia were transplanted with the product. In addition, supportive data was provided for four patients with end-stage dilated cardiomyopathy, seven patients with dilated cardiomyopathy and eight patients with ischemic cardiomyopathy. Thus, this conditional approval for heart failure due to ischemia was granted on a very modest size trial (seven patients) plus a modicum of supportive data in related indications (19 patients).

Figure 2. Conventional and new Pathways for Approval of Regenerative Medicine Products in Japan[20]

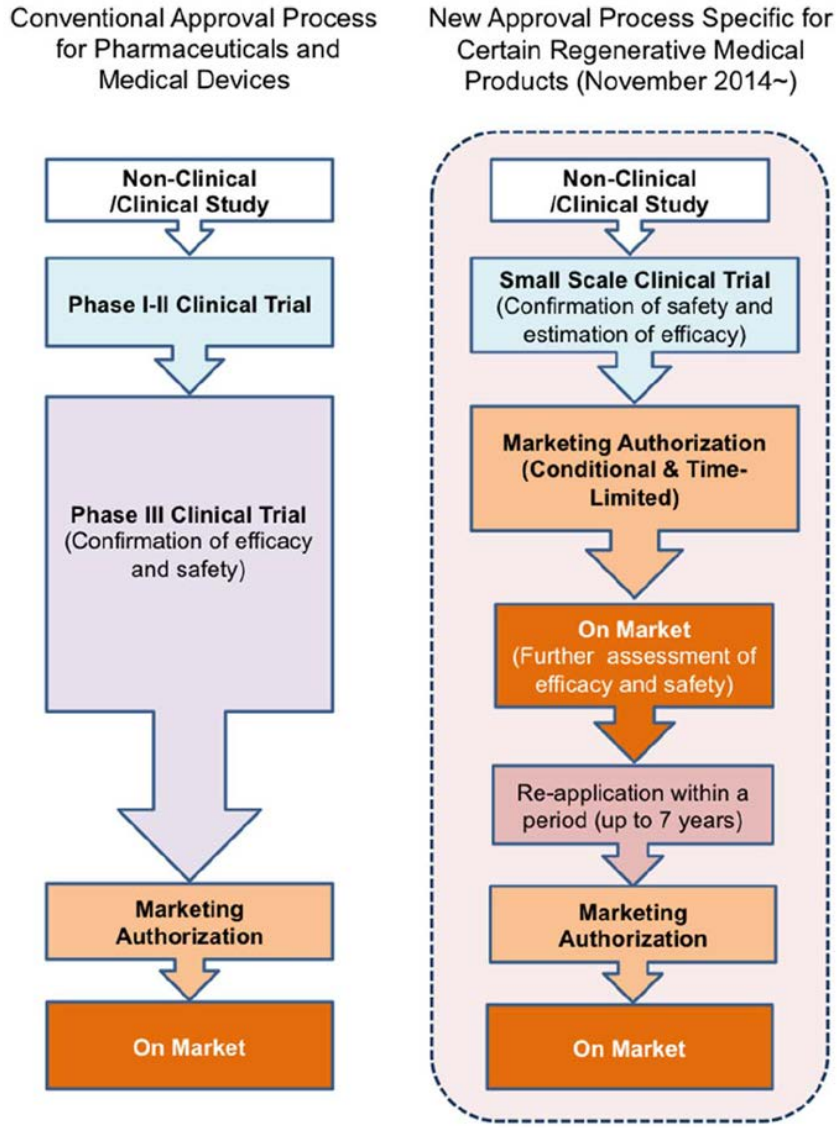


Table 4. Regenerative Medical Products Approved in Japan Since the new Regenerative Medicine Legislation

Approval Date	Brand Name (Applicant Company)	Approval Type	Product	Indication
18 September 2015	TEMCELL® HS Inj. (JCR Pharmaceuticals Co., Ltd.)	Conventional approval	Human (allogeneic) bone marrow-derived mesenchymal stem cell	Graft-versus-host disease
18 September 2015	HeartSheet® (Terumo Corporation)	Conditional and time-limited approval	Human (autologous) skeletal myoblast-derived cell sheet	Heart failure caused by ischemic heart disease
29 September 2016	JACE® (Japan Tissue Engineering Co., Ltd.)	Partial change approval (new indication)	Human (autologous) epidermis-derived cell sheet	Giant congenital melanocytic nevus

Conclusion

Following the shared award of the 2012 Nobel Prize in physiology and medicine to Shinya Yamanaka for his work on induced pluripotent stem cells, Japan embarked on a mission to become a leader in regenerative medicine so that their citizens could enjoy the most innovative and modern treatments. Accordingly, Japanese regulators established a conditional approval framework for regenerative medicines and an innovative SAKIGAKE designation procedure providing them intimate involvement in development of these products. This involvement results in a higher degree of certainty for companies developing innovative products and potentially provides more favorable financial outcomes for successful products. The new framework is a win/win for regulators and developers.

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