

EXPERT INSIGHT

Experiences from Japan: SAKIGAKE Designation System for regenerative medical products

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On April 2015, the Ministry of Health, Labour and Welfare notified the start of the SAKIGAKE designation system in Japan. SAKIGAKE is a system to put innovative medical products, including pharmaceuticals, medical devices and regenerative medical products from Japan into clinical use. Taking into account that treatment of diseases would benefit from the introduction of innovative medical products as soon as possible, development in Japan should be enhanced by implementing all relevant policies, so as to achieve the early practical application originates from Japan ahead of other countries. On November 2014, the Pharmaceutical Affairs Law was revised and renamed the Pharmaceuticals, Medical Devices and Other Therapeutic Products Act (PMD Act). This Act provides the option of a new pathway to obtain conditional and time-limited approval for regenerative medical products. Giving patients better access to innovative medical products by providing the sponsor with generous regulatory and scientific support from an early development stage was also initiated in USA in 2012 (Breakthrough Therapy Designation system) and in the European Union in 2016 (PRIME; Priority Medicines). This review describes the SAKIGAKE designation system in Japan and highlights key considerations for developing regenerative medical products based on experience of the Pharmaceuticals and Medical Devices Agency (PMDA) in consultation and review.

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On June 14, 2013, the ‘Japan Revitalization Strategy’ [1] and the ‘Healthcare and Medical Strategy’ [2] were adopted in Japan. The Government declared the promotion of the practical application of pharmaceuticals, medical devices and regenerative medical products that are the core of medical excellence, and creating cutting-edge, innovative medical products with the potential to acquire a share of the expanding global market. Based on these actions, the Ministry of Health, Labour and Welfare (MHLW) has discussed policies to promote the development of pharmaceuticals, medical devices and regenerative medical products. On June 26, 2013, the MHLW introduced the “Vision for the Pharmaceutical Industry 2013” and “Vision for the Medical Device Industry 2013”, which depicted visions for the medium- and long-term and aimed to have the pharmaceutical and medical device industries play a major role in creating innovation with international competitiveness [3].

On December 2013, the MHLW assigned Minister’s Secretariat as main charge of the Ministerial Project Team, called ‘SAKIGAKE (Forerunner initiative) Project Team’ to realize the practical application of innovative medical products, including pharmaceuticals, medical devices and regenerative medical products. It decided to plan strategies as a package covering basic research to clinical research/trials, approval reviews, safety measures, health insurance coverage, improvement of infrastructure and the environment for corporate activities, and global market acceptance.

Japan is well recognized for its strength in basic research including

life sciences, which has allowed Japanese academia to produce many promising seeds for innovative application. It has also been pointed out that a weakness is in finding a practical application for these seeds. Producing innovative medical products ahead of other countries requires a development plan and strategies from an early development stage. Government support is in place for the series of development steps from basic research through international development to nurture the seeds into ‘first in class’ innovative medical products.

When focusing on the accelerated development of innovative medical products, efforts to further enhance safety measures for these products become increasingly important. It is important to establish an environment that can facilitate substantial qualitative improvements in safety measures based on risk–benefit assessment over the entire period from the development stage and approval review to post-marketing, as well as sharing information with overseas markets to achieve acceleration of the development and global market acceptance. Based on these considerations, the SAKIGAKE Project Team introduced the ‘Strategy of SAKIGAKE’, which consists of the ‘SAKIGAKE Designation System’ and the ‘Scheme for Rapid Authorization of Unapproved Drugs’, on June 17, 2014 [4].

SAKIGAKE DESIGNATION SYSTEM

MHLW notified the start of the SAKIGAKE Designation System for pharmaceuticals on a pilot basis

on April 1, 2015 [5] and then extended it to medical devices, diagnostics and regenerative medical products. Notifications about the application of SAKIGAKE designation for regenerative medical products on a pilot basis are announced annually [6-8]. Giving patients better access to innovative medical products by providing the sponsor with generous regulatory and scientific support from an early development stage was also initiated in USA in 2012 (Breakthrough Therapy Designation system) and in the European Union in 2016 (PRIME: Priority Medicines) [9].

Criteria for designation

Regenerative medical products for diseases in urgent need of innovative therapy that may satisfy the following four conditions:

1. Innovativeness of the products, with novel mechanism of action;
2. The target medical condition should be one of the following:
 - a. serious or life-threatening medical condition; or
 - b. medical condition with persistent symptoms (conditions interfering with normal activities of daily living) for which there is no other curative treatment
3. Highly effective treatment against the target medical condition. There is no other therapy for the target medical condition, or the symptoms of patients are expected to be significantly improved through use of the product as compared to the efficacy of existing therapies (including the case where safety is expected to be improved significantly);

4. Develop the product rapidly and file an application for approval in Japan, ahead of other countries. The sponsor of the product intend to file an initial application for approval in Japan, including the case where simultaneous applications are planned to be made in both Japan and other countries.

Advantage of designation

The SAKIGAKE designation system should allow the production of innovative medical products ahead of other countries with the shortest possible development and review process. The following measures shall be used:

1. Consistent prioritized consultation by the Pharmaceutical Medical Devices Agency (PMDA);
2. Pre-application consultation in which *de facto* review is started with data that can be submitted before the application for approval;
3. Prioritized review aiming for a further reduction in the total review period (target total review time is 6 months);
4. Assigning a manager as a concierge. Concierge coordinates sponsor and MHLW/PMDA toward approval including conformity assurance, quality management, safety measures and review;
5. Strengthening post-marketing safety measures including the extension of the reexamination period.

Pre-application consultation includes the following five menus:

1. Quality;

- 2. Non-clinical;
- 3. Clinical including plan for post-marketing data collection;
- 4. Good Clinical Practice (GCP)/ Good Laboratory Practice (GLP) compliance; and
- 5. Good Gene, Cellular and Tissue-based Products Manufacturing Practice (GCTP) compliance.

After the PMDA's *de facto* review and on-site inspection, the sponsor of the product files the application for approval in Japan (Table 1).

Steps for the SAKIGAKE designation

Under the current framework, MHLW solicits candidate products that satisfy the above criteria, and conducts a hearing on the candidate products in preparatory evaluation. The potential candidates meeting these specified criteria are invited to apply as candidates for SAKIGAKE designation. MHLW evaluates the applied products based on priorities set through

review of the applications by PMDA and the products judged to be excellent are selected or SAKIGAKE designation. MHLW reports to the Pharmaceutical Affairs and Food Sanitation Council and then designation results are made public. After the three rounds of applications, nine regenerative medical products (Table 2), 16 pharmaceuticals, six medical devices and one *in vitro* diagnostic have been assigned for SAKIGAKE designation [10].

ACCELERATED DEVELOPMENT OF INNOVATIVE REGENERATIVE MEDICAL PRODUCTS

Early approval system for regenerative medical products

On November 2014, the Pharmaceutical Affairs Law was revised and renamed the Pharmaceuticals, Medical Devices and Other Therapeutic Products Act (PMD Act) [11]. Regenerative medical products are defined as:

► **TABLE 1** SAKIGAKE designation system.

Consultation with concierge	Pre-application consultation (<i>de facto</i> review)	Review (6 months)
Quality	Inquiry/answer	I/A
Non-clinical	I/A	I/A
Clinical	I/A	I/A
GCP/GLP	Preparation On-site inspection	On-site inspection
GCTP	Preparation On-site inspection	On-site inspection
	5 tracks as one package Cost: 90,000 USD	

GCP: Good Clinical Practice; GLP: Good Laboratory Practice; GCTP: Good Gene, Cellular and Tissue-based Products Manufacturing Practice.

▶ **TABLE 2****Assigned regenerative medical products for SAKIGAKE designation (as of April 2018).**

No.	Code/product name	Target condition/disease	Sponsor
First Round			
Announced date: 1 July, 2015/Assigned date: February 10, 2016			
1	STR01 (autologous bone marrow-derived mesenchymal stem cell)	Neurological symptoms and disabilities caused by spinal cord injury	NIPRO https://www.nipro.co.jp/en/
2	G47Δ (DS-1647) (Growth-controlled oncolytic HSV-1)	Glioblastoma	Institute of Medical Sciences, University of Tokyo http://www.ims.u-tokyo.ac.jp/imsut/en/ Daiichi Sankyo Co., Ltd https://www.daiichisankyo.com/
3	JRM-001 (Autologous cardiac stem/progenitor cells)	Pediatric congenital heart disease (single ventricle physiology) https://clinicaltrials.gov/ct2/show/NCT02781922?term=JRM-001&rank=1	Japan Regenerative Medicine Co., Ltd http://j-rm.com/
Second round			
Announced date: 3 October, 2016/Assigned date: February 28, 2017			
4	CLS2702C/D (Autologous oral mucosal cell sheet)	Promotion of wound healing and the prevention of inflammation and esophageal stricture after resection of cancer cells from the esophageal mucosa https://clinicaltrials.gov/ct2/show/NCT02866019?term=CLS2702C%2FD&rank=1	CellSeed Inc. http://www.cellseed.com/index-e.html
5	Dopamine neural precursor cell derived from allogeneic iPS cell	Amelioration of neurological symptoms of Parkinson's disease	Sumitomo Dainippon Pharma Co., Ltd http://www.ds-pharma.com/
6	HLCM051 (Pluripotent progenitor cell derived from allogeneic adult bone marrow)	Acute ischemic stroke https://clinicaltrials.gov/ct2/show/NCT02961504?term=HLC-M051&rank=1	Healios K.K https://www.healios.co.jp/en/
Third round			
Announced date: 5 October, 2017/Assigned date: March 27, 2018			
7	TBI-1301 (NY-ESO-1 T cell receptor gene transduced autologous T lymphocytes)	Synovial sarcoma https://clinicaltrials.gov/ct2/show/NCT03250325?term=TBI-1301&rank=2	Takara Bio, Inc. http://www.takara-bio.com/index.html
8	CLBS12 (Autologous CD34+ cells)	Critical limb ischemia https://clinicaltrials.gov/ct2/show/NCT02501018?term=CLBS12&rank=1	Caladrius Biosciences, Inc. https://www.caladrius.com/
9	AVXS-101 (Spinal Muscular Atrophy (SMN) gene therapy via AAV9)	Spinal muscular atrophy https://clinicaltrials.gov/ct2/show/NCT02122952?term=AVXS-101&rank=5	AveXis, Inc. https://avexis.com/

1. Processed (more than minimal manipulation) live human/animal cells that are intended to be used for either:
 - a. The reconstruction, repair or formation of structures or functions of the human body; or
 - b. The treatment or prevention of human diseases
2. Gene therapy

The regenerative medical products considered are mainly those satisfying unmet medical needs (serious or life-threatening illnesses). Given that, in regenerative medicine products, there is a high variability in the quality of cells, manufacturing capacity, mechanism of action, number of patients with the target medical condition, clinical positioning of products etc., it would require long-term collection of clinical data for confirmation of effectiveness and safety. The PMD Act provides the option of a new pathway to obtain conditional and time-limited approval for regenerative medical products to achieve the early practical application. To obtain conditional and time-limited approval, exploratory clinical trials are required that predict a reasonable likelihood of clinical benefit (for example, by using a surrogate endpoint). Following the conditional and time-limited approval, a confirmatory clinical study and follow-up patient safety measures are required to prepare for a further approval process within a maximum period of 7 years. Toward the full approval (second approval) review after the conditional and time-limited approval (first approval), it is necessary to construct a feasible plan to confirm

effectiveness and safety before the expiration of conditional and time-limited approval. In order to ensure that products with unconfirmed effectiveness do not remain on the market, the new regulation gives MHLW a clear legal authority to withdraw approval during the second approval process. In September 2015, HeartSheet, a skeletal myoblast sheet product for the treatment of severe heart failure, was the first product granted conditional and time-limited approval [12] (available online; for assessment report see [13]). The regenerative medical products that received SAKIGAKE designation as regenerative medical product targets for a serious or life-threatening medical condition are good candidates to obtain conditional and time-limited approval.

Points to consider: SAKIGAKE pre-application consultation

The application dossier must be well prepared, since the target total review time is 6 months for the SAKIGAKE designation products. *De facto* review through the SAKIGAKE pre-application consultation is an essential mechanism to start review/inspection as early as possible to achieve the ambitious goal of shortest review time. PMDA reviews whether the quality/non-clinical/clinical data are adequate to file the application for product approval and also helps develop the application dossier with the sponsor. The points to consider at the time of SAKIGAKE pre-application consultation from the PMDA's experience so far are described below.

Quality management system

Even if the development period is short in the case of conditional and time-limited approval, quality data, such as process evaluation, characterization, batch analysis and stability, must be included in the application dossier. A broad range of information on quality is collected from the early stage of development of regenerative medical products. As a general rule, process validation is a requirement in application of manufacturing and quality control for products to be placed on the market. However, there may be limitations on the availability of samples due to ethical aspects (e.g., issues with donor) and technologies of characterization. In addition, the process validation can be insufficient to assure quality before pre-application consultation. It is critical to ensure quality assurance by developing a flexible control strategy, based on scientific assessment of the quality risk. Verification and other methods should be appropriately utilized. Verification is the confirmation and assurance of the product quality as intended for each batch, usually applied when the elucidation of the quality control for the product could be insufficient due to the restricted conditions or technical limitation. In other words, verification could be stated to be an approach that must be taken with careful confirmation of in-process control and quality attributes that may be critical for each batch of production. Furthermore, when verification is used for quality assurance, continuous verification by following the verification master plan is required until verification becomes possible. From the point of view of quality

assurance, there is not much difference in the basic concept of verification of manufacturing of investigational products and that of the post-marketing products. However, because investigational products are manufactured at the development stage when the manufacturing methods and test methods are not established, the control strategy should be developed based on an attentive quality risk management system that takes into consideration the knowledge available on product quality and manufacturing process at that time point.

Clinical study data & post-marketing data collection

Clinical results must be adequate to describe product safety and efficacy in the application dossier. In addition, the post-marketing protocol of evaluating the effectiveness and safety is also important. If it is difficult to plan the protocol to collect clinical data for patients who have received the regenerative medicine products as well as those who have not been treated with the regenerative medicine products during the post-marketing period, it may not be possible to justify further evaluation of the effectiveness and safety. It may also not be easy to obtain conditional and time-limited approval. Since the design of the clinical evaluation in the post-marketing period and how best to demonstrate effectiveness usually depend on the individual product (in terms of the indicated use, population, mode of action and medical environment) the sponsor is also encouraged to engage in consultations.

▶ **TABLE 3****List for marketing approval products form SAKIGAKE designation (as of April 2018).**

No.	Product name	Assigned date	Approved date	Sponsor
Pharmaceuticals (2 of 16 products)				
1	RAPALIMUS GEL 0.2% (mTOR inhibitor) for angiofibroma in tuberous sclerosis	October 27, 2015	March 23, 2018	Nobelpharma Co., Ltd https://www.nobelpharma.co.jp/en/news/pdf/20180326_en.pdf
2	XOFLUZA™ Tablets 10mg/20mg (Baloxavir Marboxil) for the treatment of influenza types A and B	October 27, 2015	February 23, 2018	Shionogi & Co., Ltd http://www.shionogi.co.jp/en/company/news/2018/pmrlt-j0000003nx1-att/e180223.pdf
Medical devices (1 of 6 products)				
1	TITANBRIDGE™ for type II thyroplasty	February 10, 2016	December 15, 2017	Nobelpharma Co., Ltd https://www.nobelpharma.co.jp/en/news/pdf/20171215_en.pdf

In June 2014, MHLW reported that establishing a system and supporting environment to follow-up patients who are given regenerative medicine products is necessary to most effectively carry out clinical evaluation in post-marketing. MHLW/PMDA established a 'public patient registry system' to support a more accurate collection of clinical data for patients who applied the regenerative medicine products in post-marketing period. Such high quality data can improve medical care through allowing prompt safety measures, and also help new product development. Regenerative medical product database (DB), which plays a role of patient registration system, is defined for each product or medical treatment area, as registration items need to be set according to the target medical condition and product characteristics. Depending on each product, sponsor and relevant academic societies may collaborate to construct and operate a DB. The DBs are classified on the following three conditions:

1. A DB builds and operated by marketing authorization holder;
2. A DB built as a part of an existing patient registration system in academic societies;
3. The patient registration system that PMDA constructed as a public foundation in FY2015.

Currently, the public DB constructed by PMDA is integrated as a part of National Regenerative Medicine Database (NRMD) for post-marketing surveillance (NRMD/PMS) operated by The Japanese Society for Regenerative Medicine (JSRM). On September 2017, MHLW requested the cooperation of medical institutions for enrolling patient records to NRMD [14]. In order to evaluate medically meaningful safety and effectiveness for regenerative medical products, information on not only the patients who applied the product but also on the control group is indispensable. For this reason, it is also recommended to utilize NRMD for clinical research (NRMD/CR),

which is also a part of NRMD. PMDA discusses with the sponsor the feasibility of collecting data, as well as how to establish and operate the DB as a patient registration system to construct an information collection system for necessary post-marketing measures during the SAKIGAKE pre-application consultation.

TRANSLATIONAL INSIGHT

The SAKIGAKE designation system is enabling partnership between applicant and regulator to deliver products to patients. The SAKIGAKE pre-application consultation is an essential mechanism to start review/inspection as early as possible to achieve the ambitious goal. At the present time, the pharmaceuticals and medical

devices assigned for the SAKIGAKE designation system have been approved (Table 3) but not yet for regenerative medical products. In the near future, we hope that approved regenerative medical products utilizing the SAKIGAKE designation system will be delivered to patients.

FINANCIAL & COMPETING INTERESTS DISCLOSURE

The authors have no relevant financial involvement with an organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock options or ownership, expert testimony, grants or patents received or pending, or royalties. No writing assistance was utilized in the production of this manuscript.

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