THE EXPEDITED REGULATORY PROGRAMS FOR REGENERATIVE MEDICINES IN THE US, EU AND JAPAN

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BACKGROUND

- Regenerative medicines (RMs) constitute an emerging interdisciplinary field with intention to replace or regenerate human cells, tissues or organs in order to restore or establish normal functions[1]. It is expected to bring new hopes for disease areas with limited treatment availability[2].
- Given the limited number of RMs approved, substantial efforts were made by regulators around the world in order to accelerate the approval of RMs[3]:
  - The establishment of specific RMs legislation or framework (Table 1), and the formation of specific RMs expert committees for evidence evaluation.
  - The adoption of more flexible approaches for the assessment of market authorization application of RMs.
- Expedited programs with the purpose of enhancing the interaction between regulators and developers, as well as facilitating the approval of RMs are currently being implemented in the United States (US), Europe and Japan[4], which are defined as Regenerative Medicine Advanced Therapy (RMAT) designation, Priority Medicines (PRIME) designation and SAKIGAKE designation, respectively.

Table 1. Specific regulations/legislations for RMs in the 3 regions

Region	RMs regulation	Objectives
United States[5]	Comprehensive regenerative policy framework (November 2017)	It is intended to strike the balance between the agency's commitment to safety and advances in regenerative medicine, in a way that innovators can bring new, effective therapies to patients as quickly and safely as possible.
Europe[6]	Regulation (EC) No 1394/2007 (2007)	Proposed technical requirements tailored to RMs, in particular the type and of the degree of quality of preclinical and clinical data, necessary to demonstrate the quality, safety and efficacy.
Japan[7]	Pharmaceutical and Medical Device Act (November 2013)	Conditional, time-limited approval for a maximum of 7 years for RM demonstrating likely efficacy and confirmed safety evidence in the preliminary clinical trial.

OBJECTIVE

- This study aimed to describe the implementation of RMAT designation in the US, PRIME designation in European Union (EU) and SAKIGAKE designation in Japan, respectively.
- The characteristics of RMs granted with RMAT designation, PRIME designation and SAKIGAKE designation were investigated.

METHOD

- The official websites for Food & Drug Administration (FDA)[8], European Medicines Agency (EMA)[9] and Pharmaceuticals and Medical Devices Agency (PMDA)[10] were browsed, complemented with a literature review in order to obtain the following information related to the expedited programs in each region:
  - The date of issue; time for submission of the request; qualifying criteria; and the mechanism of expedition.
- RMs granted with PRIME designation and SAKIGAKE designation were extracted from official websites. The press releases published by the manufacturers for the RMs receiving RMAT designation were searched. The following information was extracted for products with above expedited designations:
  - Grant date; product classification; target disease areas.
- ClinicalTrials.gov[11] was searched to understand the current development stages of each RMs benefiting from expedited programs in order to predict the RMs that is going to be launched in the near future.

RESULTS

1. Comparison of the expedited programs

- The main differences between RMAT designation, PRIME designation and SAKIGAKE designation were shown in the eligibility criteria, potential benefits for eligible products and the time point for request submission (Table 2).

Table 2. Comparison of expedited programs in the US, Europe and Japan

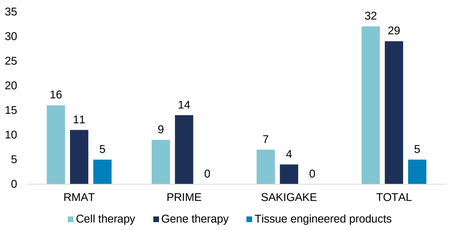
	RMAT	PRIME	SAKIGAKE
Date of issue	December 2016	March 2016	April 2015
The eligible criteria	• RMs that are intended to treat, modify, reverse, or cure a serious or life-threatening disease or condition • Preliminary clinical evidence indicates that the drug has the potential to address unmet medical needs for such disease or condition	• Offers a major therapeutic advantage over existing treatments • Benefit patients without treatment options • Shows its potential to benefit patients with unmet medical needs based on early clinical data	• Product novelty • Target disease condition should be serious or life-threatening, or have no available curative treatments • Significantly improvement in effectiveness or safety compared to existing treatments • Develop the product rapidly and file an application for approval in Japan, ahead of other countries
Product category	Exclusively applied to regenerative medicines	Biological; chemical; immunological; advanced therapy	Pharmaceutical products; medical device; regenerative medicines.
Benefits[12]	• Intensive guidelines on drug development as early as phase 1; • Early interaction to discuss potential surrogate or intermediate endpoints; • Organizational commitment involving as senior managers; • Statute addresses potential ways to support accelerated approval and satisfy post-approval requirements	• Appoint a rapporteur from CHMP or CAT • Intensive guidelines on the overall development plan and regulatory strategies • Scientific advice at key development milestones, involving additional stakeholders, such as HTA body • Potential for accelerated assessment	• Consistent prioritized consultation • Pre-application consultation • Prioritized review aiming for a further reduction in the total review period to 6 months compared to 9 months in ordinal priority review and 12 month in standard review. • Assigning a PDMA manager as concierge. • Extension of re-examination period • Potential of 10~20% premium at drug price.
Date for request submission	Request submitted along with the application of Investigational New Drug.	EMA proposed 11 deadlines for the submission of PRIME designation request in 2019	Announcements for the commencement of SAKIGAKE designation application is released annually

CAT: Committee for Advanced Therapies; CHMP: Committee for Medicinal Products for Human Use; HTA: Health Technology Assessment: PDMA: Pharmaceuticals and Medical Devices Agency; PRIME: Priority Medicine; RMAT: Regenerative Medicine Advanced Therapy

2. Characteristics of RMs benefiting from expedited programs

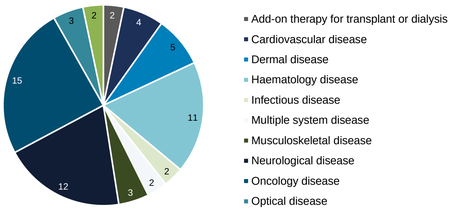
- As of July 2019, 32 RMs were granted with RMAT designation.23 RMs were granted with PRIME designation, accounting for 43.40% among all PRIME designated products. 11 RMs were granted with SAKIGAKE designation, accounting for 25.58% among all SAKIGAKE designated products.
  - 3 products (JCAR017, AT132, KB103) were granted with both PRIME and RMAT designation,
  - 1 product (AVXS-101) was granted with both PRIME and SAKIGAKE designation,
  - 1 product (HLCM051) was granted with both RMAT and SAKIGAKE designation.
  - No product was granted with all the three RMAT, PRIME and SAKIGAKE designation.
- Cell therapy represented the largest percentage of all RMs with expedited designation (Figure 1).

Figure 1. The RMs classification for RMs benefiting from expedited programs



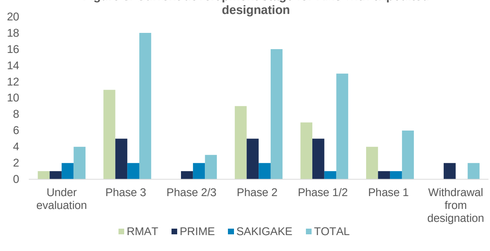
- Disease area with the largest number of RMs benefiting from expedited programs was oncology, followed by neurology and haematology (Figure 2).

Figure 2. Disease areas for the RMs with expedited designation



- RMs with orphan drug designation (ODD) accounted for 77.27% in all RMs granting with expedited designations. The number of RMs granted with ODD for each program was as follows:
  - 25 (78.13%) for RMs with RMAT designation,
  - 23 (100%) for RMs with PRIME designation,
  - 3 (27.27%) for RMs with SAKIGAKE designation.
- Three RMs with PRIME designations were approved by EMA until June 2019: Zynteglo® (29/05/2019); Yescarta® (23/08/2018); Kymriah® (22/08/2018).
- One RM with SAKIGAKE designation was approved by PMDA: Stemirac® (28/12/2018).
- No product with RMAT designation has been approved up to now. The current development stage of RMs with expedited designation was showed in Figure 3.

Figure 3. Current development stage for RMs with expedited designation



CONCLUSIONS

- Disparities were identified between RMAT designation, PRIME designation and SAKIGAKE designation in terms of time of request submission, eligibility criteria, and potential advantages granted[13].
- Collaborations between 3 regions could be beneficial to reach an agreement regarding the basic evidence requirements for products eligible for above expedited programmes.
- Thanks to expedited programmes, a faster patient access to promising curative therapies could be expected in the near future.

REFERENCES
1. Mason C et al. Regen Med. 2008;3(1):1-5.
2. Buzhor E et al.Regen Med. 2014;9(5): 649-72.
3. Coppens DGM et al. Cytotherapy. 2018;20(6):769-78.
4. Kondo H et al. Ther Innov Regul Sci. 2016;51(1):51-4.
5. Kellathur SN et al. Biologicals. 2012;40(3):222-4
6. de Wilde S et al. Drug Discov Today. 2018;23(7):1328-33.
7. Sipp D. Cell Stem Cell. 2015;16(4):353-6.
8. FOOD&DRUG ADMINISTRATION. https://www.fda.gov/home
9. European Medicines Agency. https://www.ema.europa.eu/en
10. Pharmaceuticals and Medical Devices Agency. http://www.pmda.go.jp/
11. ClinicalTrials.gov. https://clinicaltrials.gov/
12. Detela G et al. Mol Ther Methods Clin Dev. 2019;13:205-32.
13. Rosemann A et al. Regen Med. 2016;11(7):647-57

ISPOR 2019, Copenhagen, Denmark, November 2-6 2019. PBI49.