# International Standardization as the Key to Commercialization of Regenerative Medicine

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For the commercialization of regenerative medicine, it is important to strategically promote the standardization of quality control methods for cells for therapeutic use, as well as for research and development (R&D) and the protection of intellectual property rights. This article overviews the roles of international standards in market creation and trends in their development and also discusses issues to be addressed to secure the international competitiveness of Japan and Japanese companies.

## 1. Regenerative medicine ecosystem and market creation

With unmet medical needs in diseases for which no effective treatment is yet available, such as Parkinson's disease and heart failure, an environment is being prepared for the spread of regenerative medicine. In Japan, systems for early approval of regenerative medicine products and outsourcing of cell processing have been established through the "Act on Securement of Safety of Regenerative Medicine, etc." and the "Pharmaceutical and Medical Device Act" enacted in 2014, creating a legal environment for establishing regenerative medicine as a new industry.

The regenerative medicine market consists of the medical sector responsible for the provision of medical care to patients and the medical-related industrial sector responsible for the production and distribution of cells for therapeutic use and the supply of necessary equipment and consumables. Since cells for therapeutic use are produced by processing and culturing cells collected from humans, the construction of supply chains (SCs) for cells for therapeutic use is one of the important issues to be addressed in achieving the commercialization of regenerative medicine (Figure 1). Although still in their infancy, both markets are expected to grow to several tens of trillions of JPY globally over the next 10 to 20 years (Figure 2).

## 2. International standards can reduce friction in the regenerative medicine ecosystem

Regenerative medicine involves various stakeholders, such as universities, research institutes, medical institutions, pharmaceutical and related industrial companies, as well as regulatory authorities.

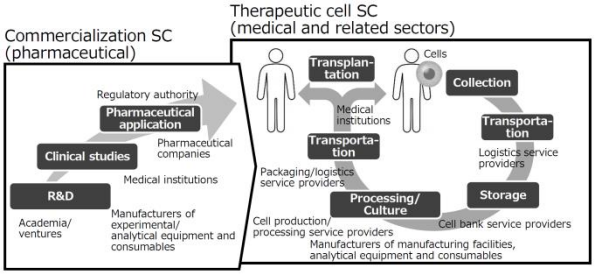


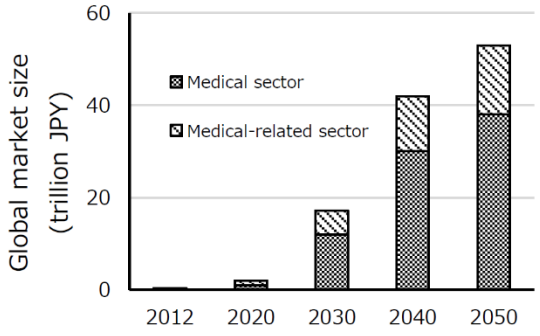

Figure 1: Supply chains (SCs) supporting regenerative medicine

Therefore, the costs for exchanges of knowledge, data and other information between different sectors, such as industry/academia/government, medical/pharmaceutical/engineering and bio/non-bio, must be reduced to achieve commercialization of regenerative medicine. The Organization for Economic Cooperation and Development (OECD) has proposed 11 mechanisms to facilitate collaboration among stakeholders and promote market development, one of which is the promotion of international standardization through consensus development [1]. Standardization is defined as "an action to reduce, simplify and organize things that can be diversified, complicated and disorganized if left unattended[2]." International standards not only serve as a "common language" among various stakeholders having unique common senses, but also streamline the social dissemination of research results by forming a global market that follows common sets of rules.

The importance of international standards is reflected in each country's policy on regenerative medicine. In the United States, "The 21st Century Cures Act" was enacted in 2016 for the promotion of the commercialization of innovative medicine, demanding the establishment of standards to streamline the launch of regenerative medicine products. Similarly, China defines international standardization as a priority issue in their "National Guidelines for Medium-to-Long-Term Development of Science Technologies" and is vigorously nurturing the human resources necessary for the development of international standards and its promotion through collaboration between the government and industry.

## 3. Overview of international standards in regenerative medicine

International standards/specifications related to regenerative medicine underwent rapid development in the 2010s, with the total number reaching about 210 by the end of 2018.

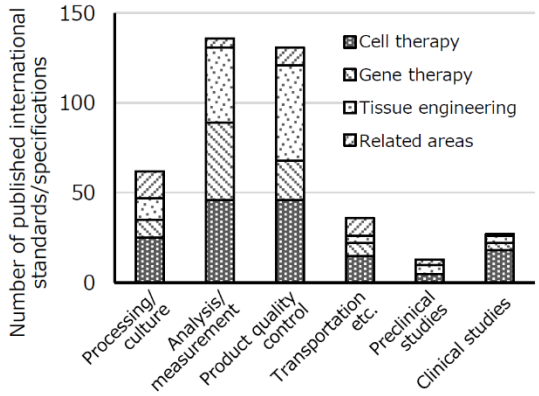



Prepared by Hitachi Research Institute based on data from the Ministry of Economy, Trade and Industry

Figure 2: Global market growth forecast for regenerative medicine

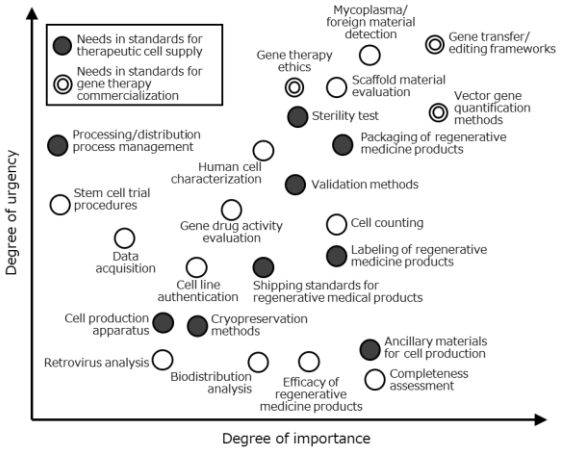
[1] International Regulatory Cooperation: Addressing Global Challenges, OECD (2013)

[2] Japanese Industrial Standards Committee




Prepared by Hitachi Research Institute based on data from Standards Coordinating Body[3]

Figure 3: Number of published international standards/specifications related to regenerative medicine




Prepared by Hitachi Research Institute based on data from Standards Coordinating Body[4]

Figure 4: Standardization needs in regenerative medicine

The results of a detailed analysis show that a significant proportion of these standards are related to the quality control methods for regenerative medicine products and related analysis/measurement methods (Fig. 3). This appears to reflect the difficulty in applying the conventional quality control methods for industrial products, which are based on the demonstration of product equivalence, to regenerative medical products comprised of variable and changeable "living cells". It should also be noted that many of the existing standards were developed for use as evaluation criteria for approval of regenerative medicine products under the guidance of regulatory authorities. This likely reflects the authority's intention to accelerate the commercialization of regenerative medicine through accelerated approval of products to which standard-based quality control methods are applicable.

As for emerging standards, with an increasing number of companies entering the therapeutic cell SC from different sectors, there is a growing need for standards that reduce barriers to their entry, including standards that define basic requirements for the manufacturing, packaging and distribution of cells (indicated by ● in Fig. 4). There is also a high need for standards that contribute to the realization of the latest R&D achievements, such as gene editing frameworks and their ethnicity, which is another feature of regenerative medicine, an area experiencing major technological innovations (indicated by ◎ in Fig. 4).

Table 1: ISO technical committees related to regenerative medicine

| Technical committee | Items considered for standardization |
|---|---|
| ISO/TC 150 SC7 | Efficacy of therapeutic tissue engineering products and general administrative affairs |
| ISO/TC 194 SC1 | Safety of biomaterials for medical devices |
| ISO/TC 198 | Sterility assurance methods for regenerative medicine products |
| ISO/TC 276 | Manufacturing process and related technologies for regenerative medicine products |

In the International Organization for Standardization (ISO), several technical committees recommend the development of standards related to regenerative medicine (Table 1). Of these committees, TC 276 Biotechnology is responsible for the development of standards related to the supply of therapeutic cell products and is currently engaged in the development of standard documents related to the manufacturing equipment, transportation methods and bacterial testing methods for therapeutic cells, whose importance was also suggested by the aforementioned needs analysis.

## 4. The current status of standardization in regenerative medicine and issues in Japan

Standardization in regenerative medicine has been driven by the motivation for market creation. However, as leading companies are launching regenerative medicine products in the market, it is expected that standardization will be promoted with the aim to establish market rules that are advantageous for nations and companies. The U.S. and China have already ramped up efforts to develop standards based on national strategies. In the U.S., the Food and Drug Administration (FDA) has organized an industry-government-academia consortium referred to the "Standards Coordinating Body", as demanded by "The 21st Century Cures Act", to promote the development of standards through public-private collaboration. In China, standardization is defined as an important element in the cell bank strategy and other major regenerative medicine strategies formulated in a top-down manner to support activities of international standardization organizations.

In contrast, in Japan, an adequate standard development system has not been established with an encompassing view of regenerative medicine. For example, the domestic committees corresponding to the four ISO technical committees shown in Table 1 belong to different bodies and are working independently from each other. Although the domestic committees are aware of the inappropriateness of the current situation for securing international leadership, they are only seeking for measures that can be implemented at the committee level, such as mutual dispatch of committee members. In regenerative medicine applications using pluripotent stem cells, on which Japan has led R&D activities, there also is movement toward standardization led by other countries. Thus, strengthening the domestic structure for standardization is an urgent task in Japan.

Given that regenerative medicine is positioned as a priority area in the "Future Investment Strategy 2017", which describes the path to Society 5.0, it is important to develop at the national level a strategy that organically integrates standardization with R&D and protection of intellectual property rights. Hitachi Research Institute continues to provide comprehensive perspectives on the commercialization and securement of competitiveness of regenerative medicine.

[3] The Regenerative Medicine Standards Landscape, Standards Coordinating Body (2019)

[4] Community Perspectives: Needed Standards in Regenerative Medicine, Standards Coordinating Body (2019)