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Abstract

Though Japan has surpassed South Korea in terms of research and development (R&D) in the area of regenerative medicine, South Korea has been more successful at commercialization. This paper focuses on the setup and operation of actual systems that consider the promotion of regenerative medicine in Japan. Analysis of the regulatory systems in Japan and South Korea shows a clear difference between the two countries, although their systems are basically the same. There are two pathways for applying unapproved drugs in clinical research, including regenerative medicine, to human subjects in Japan, whereas there is only one pathway in South Korea, where the Korea Food and Drug Administration (KFDA) is the only authority through which approval can be obtained. Japan has an additional pathway besides approval through the Pharmaceuticals and Medical Devices Agency (PMDA), if the clinical research is conducted within the framework of the Medical Practitioners Law.

The authors assume that the coexistence of the two pathways in Japan creates inefficiencies in commercializing regenerative medicine products (RMPs). Therefore, to disseminate regenerative medicine in Japan, the authors recommend combining the two pathways under PMDA authority.

1. Introduction

Expectations for regenerative medicine are broadly expanding together with public desire for improved health and amid rapid development in related disciplines. To fulfill these expectations, a number of policy steps have been taken in Japan since around 2000 to promote research related to regenerative medicine. The question becomes whether these policies can effectively achieve commercialization of regenerative medicine. Another question is whether public welfare will improve as a result of such commercialization.

To answer these questions, this paper examines a variety of literature to reveal the present status of commercialization in Japan in comparison with the rest of the world. Based on the results, it is estimated that in the research phase considerable achievements have been made in Japan. However, in terms of practical application of the research output, relatively little progress has been made. The emergence of regenerative medicine is clearly lagging in Japan in comparison to developments in other major global economies.

The complexity of introducing and establishing new technology in society can help explain this situation. A number of factors are intertwined in commercializing technology, and it is difficult to differentiate them. From an industrialization viewpoint, for instance, the social circumstances affecting business activities are key[1]. This point must be taken consideration not only in the case of regenerative medicine but for any new technology.

Regenerative medicine, on the other hand, as its name indicates, will be used in society as a medical technology. This means that the technology is commercialized under the regulatory regime that governs the medical field. This paper focuses on Japan's regulations in the medical field from the perspective of promoting the commercialization of regenerative medicine. Tremendous regulatory disparities exist between Japan and other major economies. Based on this, the current state of commercialization in regenerative medicine is considered by referring an actual case of approval review on a product that to date has only been approved in Japan.

[1] Conceição, P., Gibson, D. V., Heitor, M. V., Sirilli, G. (2001)

2. Progress of Regenerative Medicine

2.1. Transplantation of Biological Function

A healthier and longer life is probably the desire of every person at any time in any place in the world. Life expectancy in Japan today has extended significantly, and for the desire of people to enjoy fulfilling lives in good health are growing in step with the extension of their life span.

Responding to these expectations, medical care has achieved remarkable progress. New treatments for diseases once considered incurable have been found as a result of aggressive research, and have been applied in numerous medical fields. Regenerative medicine, the subject of this paper, is one such treatment. Through the human body's self-renewal abilities a lost function can be restored. Regenerative medicine, in this context, can be seen as an ultimate therapy.

The self-renewal capability of animals has been known since ancient times. The first case for the use of this capability in humans was bone marrow transplantation, which grants a hematopoietic biological function. The first human bone marrow transplant was performed in 1957, and in 1974, the world's first bone marrow bank was established in the United Kingdom. Since then, bone marrow transplants have been performed many times around the world. The world's first cord blood transplant was performed in 1988 as the same therapy, and the first cord blood bank was established in the United States in 1993.

Bone marrow transplantation is actually the transplantation of the hematopoietic stem cell itself, which is contained within the bone marrow. In contrast, new treatments are emerging in which tissues rather than cells are transplanted. Tissues are formed from cells on which biochemical or physicochemical operations are conducted; a field of technology called tissue engineering[2], which has been a highly active area in recent years.

One example of efforts in this area is for the skin. Green et al. in 1975 developed a culture method for the epidermis[3], and in 1981 autologous transplantation of epidermis was successful for burn patients using this technology[4]. Bell et al. in 1981 developed cultured skin cells with allogeneic cells[5,6], and in 1994, Brittberg et al. reported autologous transplantation of cultured chondrocytes[7]. A

[2] Ranger, R. and Vacanti, J. P. (1993)
[3] Green, H., Kehinde, O. and Thomas, J. (1979)
[4] Gallico, G. G. 3rd, O'Connor, N. E., Compton, C. C., Kehinde, O. and Green, H. (1984)
[5] Bell, E., Ivarsson and B., Merrill, C. (1979)
[6] Bell, E., Ehrlich, H. P., Buttle, D. J. and Nakatsuji, T. (1981)
[7] Brittberg, M., Lindahl, A., Nilsson, A., Ohlsson, C., Isaksson O. and Peterson L. (1994)

number of clinical cases have been reported up to the present.

2.2. Rapid Development − Technology in Infancy

The development of basic research on stem cells such as hematopoietic, neural, and mesenchymal stem cells has played a key role in the development of regenerative medicine shown in the previous subsection. The studies have helped enhance basic knowledge on biological processes such as cell differentiation and development of individuals, tissues, and cells. In the background of this research are also advances in technologies for efficient cell culture and separation.

A series of innovative research results have been produced in addition to these advances in basic research. An embryonic stem cell was established from a mouse in 1981[8,9], a primate in 1995[10] and finally a human in 1998[11]. The most relevant achievement recently in this field concerns the induced pluripotent stem (iPS) cell, which was established from a mouse in 2006[12] and a human in 2007[13,14].

Scientific knowledge on regenerative medicine continues to move forward with strong momentum. The technology is also finding practical application with the advancement of scientific outcomes. In a country or region where there is only a small body of research, with the rapid development stage in academia concentrated research activities make it possible to improve scientific output to a certain level. Developing practical applications for the outcomes, is somewhat easier in regenerative medicine as opposed to, say, aerospace in which massive systemized technologies are required, or industrial machinery, which requires extensive integration of industries.

In this context, by concentrating resources, regenerative medicine can be commercialized relatively easily in a country or region with a national financial foundation, even without sufficient large accumulation of basic research. These are the characteristics that mark regenerative medicine. In response to these technical characteristics, a great deal of research has been conducted around the world with the aim of commercializing regenerative medicine.

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[8] Evans, M. and Kaufman, M. (1981)
[9] Martin, G. R. (1981)
[10] Thomson, J. A., Kalishman, J., Golos, T. G., Durning, M., Harris, C. P., Becker, R. A. and Hearn, J. P. (1995)
[11] Thomson, J. A., Itskovitz-Eldor, J., Shapiro, S. S., Waknitz, M. A., Swiergiel, J. J., Marshall, V. S. and Jones, J. M. (1998)
[12] Takahashi, K. and Yamanaka, S. (2006)
[13] Takahashi, K., Tanabe, K., Ohnuki, M., Narita, M., Ichisaka, T., Tomoda, K. and Yamanaka, S. (2007)
[14] Yu, J., Vodyanik, M. A., Smuga-Otto, K., Antosiewicz-Bourget, J., Frane, J. L., Tian, S., Nie, J., Jonsdottir, G. A., Ruotti, V., Stewart, R., Slukvin, I. I. and Thomson, J. A. (2007)

2.3. Form of Dissemination – Supply to the Market as a Product

Transplanting human cells with a low degree of processing, such as bone marrow transplantation and cord blood transplantation, has been performed within clinical organizations as part of medical treatment. Transplantations of highly processed human cells, however, have not been able to be completed only within clinical organizations. Tissue engineering is a typical case. Autologous cultured epidermis, considered to be the first effort to commercialize regenerative medicine by tissue engineering, has been provided since 1988 to clinical organizations under the product name Epicel, by Genzyme Corporation.

As seen in this example, full dissemination of regenerative medicine beyond the area of a clinical research is usually achieved by a corporation that supplies a regenerative medicine product (RMP), a product made from human cells processed for efficacy in treatment. This requires an industry for supplying RMPs. Regenerative medicine is a "medical" treatment approach, as referred to in its name, yet the style of dissemination is the product launch in the market, which is close to the development of pharmaceuticals and medical devices.

In the manufacturing and sale of pharmaceuticals and medical devices, a certain approval is required based on a review of efficacy and safety by each regulatory authority in each country or region. For the production and sale of regenerative medicine, regulations were not clear on whether an approval was required in the early days of their introduction, since regenerative medicine differs significantly from conventional pharmaceuticals and medical devices[15]. At present, RMPs must receive approval under a category such as pharmaceuticals or medical devices before they can be manufactured and sold. The national regulatory system has largely converged on this concept.

Reviews for approval of efficacy and safety are conducted based on data obtained from clinical trials in which pharmaceuticals or medical devices under review are used on humans. Even in testing, unapproved drugs are administered to humans in clinical trials. Therefore, the clinical trial itself is under the review and approval is required, otherwise it cannot be conducted.

2.4. Pathway for Dissemination

[15] The US Food and Drug Administration (FDA), the regulatory authority in the United States, did not subject RMPs to the regulation in 1988 when Epicel was introduced. Epicel, therefore, received no regulatory approval at that time. The FDA issued market approval on Epicel in October 2007.

In addition to regulation on efficacy and safety, a government-set pricing system has been introduced for pharmaceuticals, etc. instead of pricing under the market mechanism used in most developed countries[16]. This requires a public medical insurance system that covers the entire population. In the presence of such a system, the price of pharmaceuticals is subject to policy decisions on setting the amount that insurance will pay. Such systems are deeply rooted in society and have a strong impact on the introduction of related technology to society.

The regulation and pricing stages mentioned above must be passed through in order to disseminate regenerative medicine in society with the launch of RMPs. Figure 1 shows the pathway for the dissemination of regenerative medicine. Each stage of this flow is in a series, and all stages are necessary for dissemination.

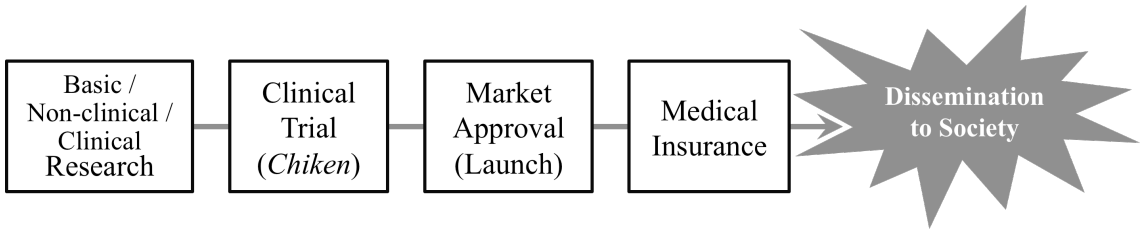


Fig. 1 Pathway for Dissemination of Regenerative Medicine

3. Present Situation in Japan

3.1. Effort in Japan – A Policy Issue

In Japan, a policy approach to promoting the commercialization of regenerative medicine has been actively underway since around 2000, amid growing interest based on the growth of scientific knowledge to enable its practical application. From the perspective of promoting research at universities, the Institute for Frontier Medical Sciences was established at Kyoto University in 1998 with the purpose of studying and its applications for the regeneration of living tissues and organs. The institute is the first established research organization in Japan specializing in regenerative medicine.

At the Ministry of Health, Labour and Welfare (MHLW), which regulates medical affairs in Japan, a

[16] The US is currently the only country among the major developed countries that does not have a medical insurance system that covers the entire population.

commitment to regenerative medicine was being actively promoted at the time. A report titled "The Future Way of the Study in the Health and Welfare Science for the 21st Century" was compiled by the MHLW's Health Science Council in November 1999. The report states that "so-called regenerative medicine, which may enable repair of damaged areas of the body and dysfunctional organs by using one's own or donated tissues and organs, is an anticipated form of treatment and its development will be advocated." In response to the report, a new category for regenerative medicine was set up in 2000 under a Health Labour Sciences Research Grant, one of the most common grants in the medical field.

For government as a whole, promotion of regenerative medicine has come to be a main policy issue. On the occasion of the new millennium in 2000, the Japanese government established the "Millennium Project," a policy package with the justification that: "in response to challenges humans are facing, we will undertake technological innovation for creating new industries." Promotion of regenerative medicine is advocated within this. Specifically it states that "regenerative medicine for bones and blood vessels will be achieved using self-regeneration ability without rejection based on elucidation of biological functions such as generation."[17]

The BT Strategy Council was also set up by the Prime Minister in July 2002 from a standpoint of "strengthening industrial competitiveness and improving people's lives by industrializing and commercializing the remarkable achievements of biotechnology."[18] "Biotechnology Strategy Outline,"[19] compiled by the Council in December 2002, states that the direction is "toward the realization of regenerative medicine to promote research for the regeneration of organs along with elucidation of the mechanism for generation and regeneration."

A certain governmental budget has been allocated to various kinds of R&D projects via the MHLW, the Ministry of Education, Science and Technology and the Ministry of Economy, Trade and Industry under these government policies.

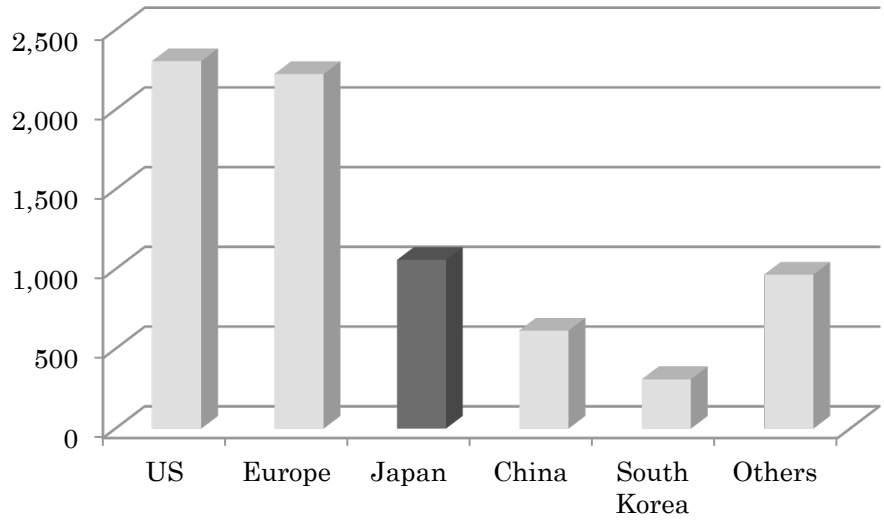
3.2. Research Results - Numbers of Papers

As shown in the previous subsection, the promotion of regenerative medicine has been raised as a government-level challenge in Japan, and related research has been promoted for its realization. The

[17] "The Basic Framework and Planning Policy for the Millennium Project" (October 9, 1999, Prime Minister's Decision)
[18] "Holding the BT Strategy Council" (July 7, 2002, Prime Minister's Approval)
[19] "BT Strategy Outline" (December 6, 2002, BT Strategy Council)

question is then raised as to how the results of these efforts should be evaluated. From this perspective, the situation of the world's research on regenerative medicine was examined via trends of papers in this field. The Japan Patent Office (JPO) in 2009 conducted a detailed study on the world's research and patents on regenerative medicine[20]. The following is analysis, based on the JPO survey[21], of research papers published during 2004-2007 related to regenerative medicine.

Figure 2 shows the number of papers per country or region of the research institute to which each paper's lead author belongs. The United States is first, with 2,304 of 7,472 papers, or 31%. Europe[22] is second with 2,223 (30%). Japan is third with 1,058 (14%).



Source: Based on data from JPO (2009)

Fig. 2 Number of Papers on Regenerative Medicine (2004-2007)

Regarding the contents of the papers, regenerative medicine-related technology is broadly divided into three categories of basic technology, applied technology and supporting technology. Basic technology is a technique for manipulating cells that is critical and fundamental for realizing regenerative medicine. This category specifically consists of techniques such as separation, purification, cultivation, growth, differentiation, modification and preservation of cells and the

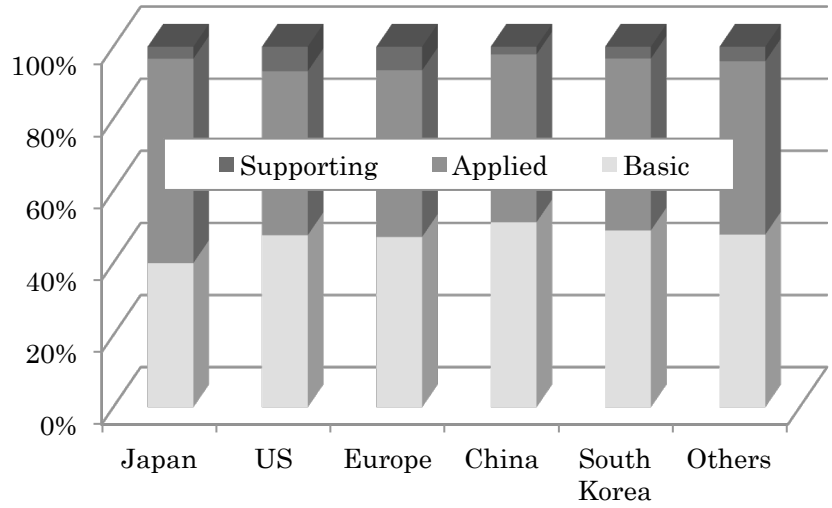
[20] JPO (2009)

[21] Regenerative medicine-related articles published in journals published in English in 2004-2007 (review, commentary and presentations are excluded) are extracted by MEDLINE. The search was conducted September 8, 2008, with 12,686 papers extracted. Based on the abstract contents, papers not included in the field of regenerative medicine were excluded and analysis was conducted on the remaining 7,472.

[22] In this article, Europe consists of signatories to the European Patent Convention as of July 2008, namely the following 34 countries: Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Liechtenstein, Lithuania, Luxembourg, Malta, Monaco, Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, Switzerland, Turkey, and the United Kingdom.

technology of related equipment.

Applied technology refers to technologies such as transplantation of cells and scaffolds, administration of the inducer and the combination of these, and the formulation of functional structures by using cells in vitro and its utilization for medical treatment; technologies assumed to apply practically for humans. Supporting technology is for implementing regenerative medicine safely and effectively; consisting of packaging, transport, safety evaluation and quality control for therapeutic cells, as well as industrial cell culture systems. Figure 3 shows the numbers of published papers by technology category.



Source: Based on data from JPO (2009)

Fig. 3 Papers by Ratio of Technology Category

Looking at the context of the research phase of these three classifications, basic technology corresponds to the basic and non-clinical research stage. Clinical research is included in applied technology. Research required in the commercialization stage can be considered to correspond to supporting technology. There is no extreme difference in the proportions of each category among country or region, but the United States and Europe have a greater ratio of supporting technology. Japan is characterized by a large proportion of applied research.

3.3. Status of Products Launched

The next area examined was commercialization of regenerative medicine, a practical objective of the

research. The situation can be estimated from the number of RMPs on the market. A current view of the entire world shows that only three kinds of RMP (skin, cartilage, and bone) organized from cells by tissue engineering have been identified in the market. The number of RMPs on the market is shown in Table 1 by the developers' country or region.

Regenerative medicine has been practiced in various ways such as not only transplanting cells as a form of tissue or organ but also transplanting them as a form of the cells themselves. Cells are thus also considered a kind of RMP[23] even though they are not organized as a form of tissue or organ. The status of the use of RPMs including this kind is difficult to grasp clearly since some are not used as marketed products but instead used as in-house processed materials. For this reason, RMPs shown in Table 1 exclude products as a form of cells.

Table 1 Number of RMPs Launched

	USA	Europe	Japan	South Korea	Others	Total
Skin	5	4	1	4	2	16
Cartilage and bone	1	12	-	3	1	17
Total	6	16	1	7	3	33

Note 1: As of December 2009

Note 2: RMPs shown in the table are limited to those organized as a form of tissue or organ by using tissue engineering.

Note 3: Companies with multiple nationalities are categorized according to the nation in which the major development was carried out.

Source: Created by the authors based on data from company homepages, Mitsubishi Chemical Techno-Research Corporation (2009), Korean Ministry of Education, Science and Technology (2009), etc.

Comparing the situation shown in Table 1 with the research output described in the previous subsection, it is understandable that the volume of research conducted on supporting technology is far less than research done on basic and applied technologies. This is because regenerative medicine has not been fully introduced yet, but anticipation is growing. Research on supporting technology is mainly done in the United States and Europe, which can be understood as a result of the introduction of regenerative medicine proceeding at a faster pace in those regions.

[23] Hematopoietic stem cell transplantation (bone marrow transplant, cord blood transplant, peripheral blood stem cell transplant), conventionally practiced in medicine, is usually categorized apart from the regenerative medicine segment.

While holding the fifth position in research output, South Korea is noteworthy for its number of marketed RMPs. From a considerable volume of research conducted in South Korea, as shown in Figure 2, it is reasonable to anticipate that a certain number of products will be launched; however, it is hardly possible to anticipate the actual number. On the other hand, Japan is quite the opposite with only one RMP marketed despite holding third position in terms of research output.

3.4. Japan's Situation in Detail

As shown above, just one RMP has been launched in Japan, which is strikingly low relative to the amount of research being done. In the dissemination pathway shown in Figure 1, this situation means the uppermost flow of the research stage is heavy but the lower flow of the market approval stage is light. The question is then, what is happening in the clinical trial stage, which is located between the two stages? This subsection considers Japan's situation in the dissemination of regenerative medicine from this perspective.

South Korea appears similar to Japan in terms of promoting research, following after the US and Europe. As described above, a great deal of research has been conducted and many RMPs have been launched recently in South Korea. It is helpful to compare Japan and South Korea to deepening the understanding of Japan's situation.

In both Japan and South Korea, RMPs are not allowed to manufacture or sell unless approved by the regulatory authority. Table 1 shows the status of market approval for RMPs in the two countries. Autologous cultured skin by Japan Tissue Engineering Co.,, Ltd. (J-TEC) is the only case of an RMP approved in Japan. In contrast, three companies have launched four RMPs in skin and two companies with three RMPs in cartilage and bone in South Korea. This means five companies have received market approval for seven products. In terms of an RMP as a form of cell itself, which is excluded in Table 1, no product has yet been approved in Japan while five have been approved in South Korea. Most of the approved products in this form mainly involve activated lymphocyte for cancer treatment.

Market approval is supposed to be given based on the authority's review, in which data obtained from clinical trials must be used. The discussion then becomes the situation of clinical trials. Table 2 shows clinical trials on RMPs in Japan and South Korea, including products in the forms of not only tissues or organs, but also cells themselves. Here we see a much greater difference between the

countries than with market approval.

The launch of RMPs must proceed through the stages shown in Figure 1. The commercialization of regenerative medicine, therefore, is highly dependent on how many products or product candidates are on this track. There are only few candidates at the clinical trial stage in Japan, which seems to contradict the current state of research being conducted. Given that the pathway is a series, it is possible to say that the low number of market approvals is caused by the low number of clinical trials. This situation has become prominent in Japan when compared to South Korea, for which the absolute amount of research has been greatly surpassed by Japan. This situation thus raises the question of what exactly is going on.

Table 2 Clinical Trials in Japan and South Korea

Phase	I/II	III	Finished	Total
Japan	1	-	1	2
South Korea	18	5	-	23

Note: As of December 2009

Source: Kurata, K. and Choi, Y.-H. (2010)

4. Differences in the Regulatory System

4.1. Japan - Two Pathways Exist

Based on the discussion in the previous section, this section examines the regulatory system for market approval, especially in terms of conducting clinical trials. As described several times, market approval is required from the regulatory authority if drugs are to be introduced. In Japan, the MHLW bears this responsibility[24]. In the review process for approval, clinical data are required. This data is collected in clinical trials that are conducted according to the standards set by the regulatory authority based on the Pharmaceutical Affairs Law (PAL)[25]. This procedure for producing new drugs is basically universal.

[24] Article 14, paragraph 1, Pharmaceutical Affairs Law
[25] Article 14, paragraph 3, Pharmaceutical Affairs Law

These clinical trials are called *chiken* in Japan[26]. The MHLW sets rules and procedures covering various matters in conducting *chiken*, from perspectives such as the protection of patients' rights, maintaining safety, and keeping scientific quality and data reliability[27]. When conducting *chiken*, a prior notification to the MHLW is required[28]. The MHLW then investigates this for adequacy of content and gives instruction if necessary[29].

Both the review for market approval and investigation for *chiken* are supposed to be carried out by the MHLW, but the Pharmaceuticals and Medical Devices Agency (PMDA) can also play the same role[30]. The application and notification are, in fact, actually submitted to the PMDA. When receiving the application or notification from an applicant, the PMDA will conduct necessary review or investigation, and reports the result to the MHLW. On receiving the result, the MHLW gives approval after consultation with the Pharmaceutical Affairs and Food Sanitation Council. The PMDA is an independent administrative agency under the MHLW, and is considered to play a pivotal role as a regulatory authority in Japan concerning the review and investigation process.

However, another pathway exists besides *chiken* for the administration to humans of unapproved new drugs. Doctors are supposed to conduct their medical practice under the Medical Practitioners Law (MPL)[31]. A doctor's act of producing unapproved drugs and administering them to patients is regarded as medical practice under the law, and so is not subject to PAL. This means such actions can be taken without the regulatory authority's approval. When this is conducted as clinical research, the head of the clinical research organization is typically required to issue permission with the consent of the Internal Review Board set up within the organization based on the "Ethical Guideline for Clinical Research"[32]. This action is then not incorporated into the strict framework of *chiken*. The guideline is just a guideline, and there is no legal obligation to follow it.

As is clear from the above, there are two pathways through which clinical actions are conducted for the development of new drugs. One is *chiken*, or a clinical trial in which data is collected to obtain market approval in accordance with PAL. Another is clinical research conducted as medical practice under MPL. Of course the former pathway must be taken in order to launch a drug. The PMDA could conduct the investigation on the adequacy of the *chiken*, and so the PMDA also reviews data obtained from *chiken* for market approval. However, the PMDA will never take part in the clinical research conducted under MPL.

[26] Article 2, paragraph 16, Pharmaceutical Affairs Law
[27] Article 1, Ministerial Ordinance for the Good Clinical Practice
[28] Article 80.2, paragraph 2, Pharmaceutical Affairs Law
[29] Article 80.2, paragraph 3, Pharmaceutical Affairs Law
[30] Article 14.2, paragraph 1 and Article 80.3, paragraph 1, Pharmaceutical Affairs Law
[31] Article 17, Medical Practitioners Law
[32] MHLW (2003)

4.2. Regenerative Medicine

In addition to the usual procedure described in the previous subsection, additional procedures have been imposed for clinical trials on regenerative medicine based on the 1999 notice[33] issued by the MHLW. Specifically, "those who intend to commission the execution of *chiken* for medical devices using cells or tissue" are requested to acquire "confirmation on safety and quality from the MHLW prior to conducting *chiken*[34]." This action is called a confirmation application. The confirmation application is submitted to the PMDA, which reviews it based on the "Quality and safety assurance of pharmaceuticals manufactured using human- or animal-derived components as raw materials" (Notification no. 1314)[35].

Even for clinical research not aiming at market approval, since 2006 additional procedures have been imposed on that which covers regenerative medicine. In clinical research in which "human stem cells are transplanted into the human body to treat disease,"[36] the head of the clinical research organization is required to hear the opinion of the MHLW based on the "Guidelines on Clinical Research Using Human Stem Cells (Guideline on Human Stem Cells)"[37]. In the hearing process, the MHLW reviews the plan of the clinical research from a safety perspective based on Notification no. 1314, as with the *chiken* by the PMDA[38].

Clinical research reviewed by the MHLW based on the Guideline on Human Stem Cells, has only been conducted in 13 cases with 26 facilities[39] since September 2006 when the guideline went into force[40]. On the other hand, the guideline also states that it "does not apply to clinical research already undertaken prior to the enforcement of the guideline,"[41] and more than 130 cases of clinical research have been conducted to date under the exemption[42]. Much of this research currently being

[33] Director-General, Pharmaceutical and Food Safety Bureau, MHLW (1999)
[34] Director-General, Pharmaceutical and Food Safety Bureau, MHLW (1999)
[35] Director-General, Pharmaceutical and Food Safety Bureau, MHLW (2000)
[36] Chapter 1 General Provisions, Section 3 Scope of Application 1, MHLW (2006)
[37] MHLW (2006)
[38] The case is in fact judged based on Annex 1 of Notification no. 1314, "Basic concepts for the handling and use of drugs and devices utilizing cells or tissues" and Annex 2, "Guidelines for assurance of quality and safety of drugs and devices processed from cells and tissues of human origin." Regarding Annex 2, revised versions were issued in February 2008 (Director-General, Pharmaceutical and Food Safety Bureau, MHLW [2008a]) and September 2008 (Director-General, Pharmaceutical and Food Safety Bureau, MHLW [2008b]). Consequently, Annex 2 of Notification no. 1314 has been abolished.
[39] As of November 2009
[40] http://www.nihs.go.jp/cgtp/cgtp/sec2/ct_prtcl/prtcl-j.html Last accessed on September 3, 2011
[41] Chapter 1 General rules, Paragraph 3 Scope, Details 1, Guidelines on Clinical Research Using Human Stem Cells
[42] http://www.nihs.go.jp/cgtp/cgtp/sec2/ct_prtcl/prtcl-j.html Last accessed on September 3, 2011

conducted is considered to be performed this way[43].

Clinical action concerning regenerative medicine is considered to require more rigorous examination than usual even if the purpose of the action is for regulatory approval or research as part of medical practice. The examination criteria for both are given in Notification no. 1314. However, a rigorous examination process was introduced in 1999 for clinical trials and in 2006 for clinical research. This represents a significant time lag. As previously mentioned, much of the research being performed uses the exemption. Moreover, the reviewer is different in each case. The PMDA is in charge of clinical trials, or *chiken*, and the MHLW covers clinical research; thus duplicate pathways remain.

4.3. South Korea

The regulatory steps are basically the same in South Korea. South Korea's regulatory authority for pharmaceutical affairs is the Korea Food and Drug Administration (KFDA). For the launch of pharmaceuticals and medical devices, it is necessary to obtain the KFDA's market approval after its review[44]. RMPs are treated in the same manner.

In the review process to obtain the KFDA's market approval, data from the clinical trial are required. In conducting clinical trials, unapproved drugs are administered to humans. In South Korea, KFDA approval is also required for administration to humans of unapproved drugs[45]. To this end, for the practice of clinical trials, application for an investigational new drug (IND) must be submitted to the KFDA, and its approval must be obtained in advance[46].

The KFDA's approval is also required for clinical research, which does not seek market approval directly, as long as unapproved drugs are administered to humans. In doing so, IND application is supposed to be submitted to the KFDA as in clinical trials. There are, however, two kinds of approval: IND approval for commercialization aiming at market approval, and that for research objectives. The rigor of the examination differs between the two[47].

Behind the KFDA's review for both clinical trial and clinical research is a fundamental belief that an

[43] The Guidelines on Clinical Research Using Human Stem Cells was fully revised on November 1, 2010, and then the escape clause was deleted.
[44] Article 31, Korean Pharmaceutical Affairs Law
[45] Article 34, Korean Pharmaceutical Affairs Law
[46] Details of the review are given in KFDA (2009) and KFDA (2008).
[47] The same documents are basically required to be submitted for the application for research IND as those for that of commercial IND based on KFDA (2009). However, it is possible to simplify document submission for the application for research IND based on Article 7 of KFDA (2009).

adequate examination must be necessary from the viewpoint of safety when unapproved drugs are administrated to humans[48]. As mentioned, there are two types of approval. Approval for commercial IND is mainly applied for collecting the necessary data that are used for market approval. Approval for research IND is applied for research activities mainly conducted in clinical research institutes such as medical schools. Criteria differ according to each approval's objectives. However, in terms of the act of administering unapproved drugs to humans, the activity plan, irrespective of the purpose, must go through review under the KFDA as a regulatory authority.

4.4. World Situation – Single Pathway

It is clear from the above that the pathway to administer unapproved drugs to humans is unique in South Korea. Comparing the regulatory frameworks of Japan and South Korea, a large difference can be cited in this regard. Though differences exist among major countries such as the United States and EU member countries in the details of their regulations, it is almost the same that regulatory approval by the authorities is required when unapproved drugs are administered to humans in any clinical research, as well as clinical trials[49].

Based on the above discussion, Figure 4 shows a conceptual framework of regulations for RMPs in Japan and South Korea.

[48] Based on an interview with a KFDA reviewer

[49] In the United States, application for IND is required to the regulatory authority when administrating unapproved drugs to human. This follows a series of legal actions such as the Kefauver-Harris Amendment established in 1962. In Europe, the EU clinical trials directive (Directive 2001/20/EC of the European Parliament and the Council of 4 April 2001 on the approximation of the laws, regulations and administrative practice in the conduct of clinical trials on medicinal products for human use) was issued in 2001, in which the initiation of clinical trials requires an approval from the regulatory authority. EU member countries are aiming to achieve implementation of domestic measures for the directive. Not only clinical trials for the purpose of regulatory approval but any type of clinical trial such as non-commercial is subject to such legal actions in the US and European countries.

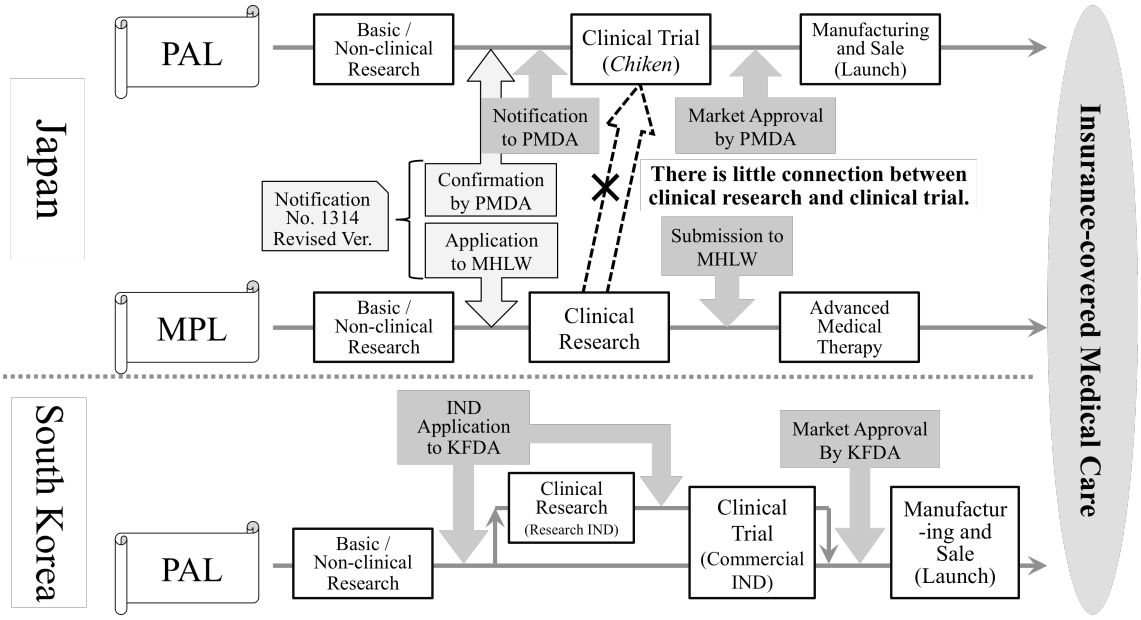


Fig. 4 Conceptual Framework of Regulations

5. What Happens

5.1. University as a Main Player in Clinical Research

As seen before, Japan has actively promoted research aimed at commercialization of regenerative medicine. In terms of research output, Japan is number three in the world after the United States and Europe. As described in subsection 3.2, many papers have been published in the category of applied research in Japan, which means there may be a certain amount of clinical research being conducted there.

Table 3 shows the attributes of the top 50 organizations according to the number of papers published in the field of regenerative medicine. Most of these organizations are universities, with a small representation by public research institutes. Companies do not appear. This can be understood as a reflection of the characteristics of regenerative medicine, as described in section 2, in that it is based on rapidly developing biotechnology and required to be adapted for humans as a form of medicine.

Table 3 Attributes of World's Top 50 Institutes for Regenerative Medicine

	University	Public institute	Total
US	19	1	20
Japan	11		11
Europe	7	2	9
China	5		5
South Korea	3		3
Others	3		3

Source: Based on data from JPO (2009)

On the other hand, the commercialization of regenerative medicine, which means providing RMPs to the market after receiving market approval from the regulatory authority, is expected to be conducted by the private sector. It can therefore be said that clinical trials under the regulatory legislation are connecting these universities with the private sector as well as connecting these two stages. As we have seen, however, only a small number of clinical trials on regenerative medicine have been conducted thus far in Japan, and it is hard to say the two are smoothly connected.

Focusing on details of the regulatory system in Japan with the understanding discussed above, a critical fact is found in that clinical trials and clinical research are conducted under completely different regulatory systems. Unlike the rest of the world, Japan has two pathways for administering unapproved drugs to humans for the development of new drugs including RMPs. Another important fact we find is that clinical research is not connected to clinical trials in Japan. The question then is how the existence of the two pathways affects this fact.

5.2. Duplex Pathways Unconnected

As noted above, most of the organizations conducting research on regenerative medicine are universities. This situation is common to the United States, Europe, South Korea, and Japan. In an institute like a university, the researcher's motive is to publish the research results in an academic paper. The activity is of course underpinned by the hopes that the new therapy will eventually become widespread and used to help patients.

In clinical research, the administration of unapproved drugs to humans is naturally practiced.

Clinical institutes will apply to the regulatory authority for permission of the act if approval is necessary, and the regulatory authority will issue approval after due examination. In the examination process, the regulatory authority comprehends the specific case and requests changes to the research plan if necessary. Conversely, an application is not made if these procedures are not required for the system. As a result, the regulatory authority will have no comprehension of the clinical research being conducted.

This situation has only recently emerged. In Japan, as mentioned above, clinical research organizations such as universities do not need to submit applications or acquire approval from the regulatory authority in their practice of clinical research. As a result, despite being quite similar in terms of administering unapproved drugs to humans, clinical research and clinical trials are regarded as completely different acts under different systems and neither will be systematically related.

For regenerative medicine, and in comparison with drugs and medical devices, the need to connect research to clinical trials is also relatively low for clinical research organizations given the technical characteristics. It is very difficult for clinical research organizations to themselves manufacture drugs that consist mainly of chemical compounds and medical devices that have a mechanical structure. Therefore, collaboration with outside companies is necessary to enable manufacturing and the provision of drugs and medical devices to the organization. This type of cooperation is expected to have a direct link with clinical trials by companies seeking to commercialize drugs or medical devices.

Clinical research organizations can manufacture RMPs relatively easily. Typical examples are RMPs with low degrees of cell processing that are manufactured within clinical research organizations as a medical practice and administered to humans for treatment. Clinical organizations can also readily manufacture well-organized RMPs through various degrees of tissue engineering, in contrast to manufacturing of drugs' chemical compounds and medical devices' mechanical structures. Thus it becomes common for clinical organizations to manufacture RMPs by themselves without the involvement of external companies and administer them to humans. Therefore there are few expectations of related clinical trials by external companies.

5.3. J-TEC – Approved with Only Two Cases

In light of the items discussed in the previous subsection, we can examine the actual case of the autologous cultured epidermis by J-TEC named JACE. This is the only case to receive approval in

Japan as an RMP. Table 4 outlines this approval. Remarkably, there were only two patients in the clinical trials. This low number of cases prompted significant debate, not only in the examination of regulatory approval, but even in the post-approval review of insurance coverage.

Table 4 Outline of Market Approval for JACE

Adaptable Case	Extensive severe burns with no donor area obtained for autologous skin grafting, as well as over 30% of the total body surface area affected by degree II or III deep burn wounds
Method of Clinical Trial	Multicenter uncontrolled open-label trial
Number of Cases	2
Approval Condition	Post-market clinical trial (10 cases) and drug use survey on all patients
Fast Track	Yes

Source: Created by the authors based on PMDA (2007), etc.

Regulatory approval is deliberated in the Pharmaceutical and Food Sanitation Council in the MHLW after the PMDA examination, and eventually goes through the MHLW approval process[50]. The published minutes suggest there was discussion about the number of clinical cases. Clearly doubt was raised about approval with such a small number. Responding to this doubt the Council secretariat, which is served by the MHLW, replied that this was a "very special case" and a post-market clinical trial was mandated[51].

The lack of cases can also be considered as influencing the discussion on whether medical insurance will cover the product. Medical insurance finally became applicable for JACE under certain conditions. Coverage is limited to treatment practiced only in facilities that meet certain criteria. Moreover, a detailed record of the patient's condition must be attached to a reimbursement claim[52].

After winning regulatory approval, it took about a year and a half for JACE to become applicable under medical insurance, in contrast to the usual six months. The Japan Medical Association's

[50] In fact, the deliberation is supposed to take place in the Subcommittee on Medical Devices and In Vitro Diagnostics under the Pharmaceutical and Food Sanitation Council.
[51] Minutes of the Subcommittee on Medical devices and In Vitro Diagnostics, Pharmaceutical and Food Sanitation Council, August 23, 2007
[52] Minutes of the General Meeting of the Central Social Insurance Medical Council, December 17, 2008

Questionable Interpretation Committee was said to have been reluctant to apply medical insurance based on the "lack of evidence of clinical effectiveness and safety grounds because of fewer cases."[53]

The constraints imposed on insurance coverage as well as the delay in insurance applicability created significant economic loss for J-TEC[54]. The presence of only two patients in clinical trials not only created a difficult approval for the MHLW, but also had a large impact on the business of J-TEC.

5.4. Clinical Research Unutilized

A question that is naturally raised is whether other clinical cases use the same technique as JACE in Japan. JACE is a Green-type autologous cultured epidermis[55]. Feeder cells have been transferred by Howard Green, the developer[56]. A great deal of clinical research in Japan uses a Green-type autologous cultured epidermis, reportedly the same as that of J-TEC. In the clinical research lead by the Department of Dental Surgery in the School of Medicine at Nagoya University, since 1995 more than 80 cases of using Green-type autologous cultured epidermis have been reported by six clinical organizations[57]. Since 1985 more than 550 cases of Green-type autologous transplantation of epidermis have also been carried out in the Department of Plastic Surgery of the St. Marianna University School of Medicine (in Kanagawa, Japan)[58,59].

While there have been many clinical cases, the PMDA's review report on JACE mentions no specific information on any of them. The report notes questions and answers between the PMDA and J-TEC regarding efficacy and safety of JACE. It states that JACE is a "Green-type autologous cultured epidermis developed under technology transfer from Department of Dental Surgery, School of Medicine, Nagoya University [omitted] manufacturing process is not identical but similar [to Nagoya University][60]." Meanwhile, there is not mention of the 80 clinical cases at Nagoya University. Of course, there is no reference to the cases at the St. Marianna University School of Medicine either.

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[53] *Nikkei Biotechnology & Business* issued June 2, 2008, p. 13
[54] *Nikkei Biotechnology & Business* issued October 26, 2009, p. 13
[55] Cultured epidermis using mouse embryo-derived cells as a feeder developed by Green et al. of Harvard University in 1975 is generally called "Green-type cultured epidermis."
[56] http://www.jpte.co.jp/business/regenerative/cultured_epidermis.html
[57] Ueda, M., Sumi, Y., Mizuno, H. and Hata, K. (1998)
[58] http://www.marianna-u.ac.jp/hospital/sinryou/shinryouka_20.html Last accessed on September 3, 2011
[59] http://www.jpte.co.jp/business/regenerative/interviews.html Last accessed on September 3, 2011
[60] PMDA (2007)

Clinical research results were not utilized in the examination at all, and it is of course obvious that data obtained in the clinical research were not used in the regulatory reviewing process. Such results are not from clinical trials in which every procedure must meet a strict protocol set by the regulatory authority but from clinical research in which no legal framework is imposed. Yet still, why was there no reference? Also, why is there no collaboration between J-TEC and Nagoya University or St. Marianna University in conducting J-TEC's clinical trial even though J-TEC has introduced the technology from Nagoya University and Professor Kumagai of St. Marianna University is serving as J-TEC's technical advisor[61]?

It is difficult to answer these questions directly. First it must be said the PMDA is not in a position to grasp the situation of clinical research being conducted, and there are no measures for acquiring comprehensive information on clinical research. The framework of clinical research, not clinical trials, is also said to be enough for Nagoya University and St. Marianna University to practice clinical application of their research under Japan's regulatory system as long as they are clinical organizations. There is no need or motivation to deliberately work with a framework of time- and effort-consuming clinical trials. The concept described in subsection 5.2 may give a clear example of Japan's only approved RMP.

Under these circumstances, it seems that it was extremely difficult for J-TEC to accumulate clinical cases and the PMDA had no choice but to give approval with only two cases in clinical trials. Amid the government's high expectations for regenerative medicine was the desire to see specific results. This may have placed strong pressure on the PMDA to give early approval, thus approval was given with the conditions of a drug use survey on all patients and 10 cases of post-market clinical trials. The granting of approval for JACE could be seen as a consequence of the PMDA's best efforts under the current system given the institutional reality of two divided pathways.

6. Conclusion - The Ideal Climate

6.1. Exit for Second Pathway

Japan's medical system provides an exit of diffusing and utilizing the fruits of clinical research for patients. This exit is considered to be not the launch of an RMP but rather the dissemination of regenerative medicine as a self-contained medical practice conducted within a clinical organization.

[61] http://www.jpte.co.jp/business/regenerative/interviews.html Last accessed on September 3, 2011

This exit comes down to implementation of a clinical organization-based treatment under the "advanced medical therapy" system. In this system, the clinical organization certified by each advanced therapy can practice the therapy in combination with other therapies already covered by medical insurance. Otherwise, even insurance-covered therapies will not be covered under Japan's medical insurance system if practiced in combination with uncovered advanced therapies. This system is said to be the exit for the second pathway.

The primary focus of the advanced medical therapy system is not on products such as RMPs but on medical techniques. This pathway is expected to play a role in terms of dissemination for therapy that will not necessarily require RMPs during its practice. Regenerative medicine, however, generally requires RMPs for its treatment. Even if regenerative medicine becomes subject to the advanced medical therapy system, the supply of RMPs, namely the series of cell processing, is supposed to be practiced by medical doctors within clinical organizations under the system.

In this process, cell isolation, culturing and processing are purely an engineering operation that will never come into contact with patients. Non-medical practices based on both hard and soft aspects are needed. These include facility preparation in terms of ensuring safety to minimize the risk of viral infection, implementation of appropriate management and placement of personnel with cell treatment skill. It is difficult for each clinical research organization and even medical institutions to prepare these aspects independently. This situation is not efficient from the viewpoint of allocation of limited medical resources.

For dissemination of regenerative medicine, it must be realistic to commercialize RMPs outside the medical organization and supply them to the medical arena[62]. In other words, it is not easy to disseminate regenerative medicine if following the second pathway leads to self-contained implementation as a medical practice within medical facilities.

6.2. Solution Required - Integration of Pathways

The dissemination of regenerative medicine to society requires going through the first pathway shown in Figure 7. While much of the clinical research on regenerative medicine has no clear exit, there is a strong requirement to connect its output with the exit as a product launch for dissemination. Cases conducted by the Nagoya University School of Medicine and St. Marianna University School of Medicine are seen as positive, individual initiatives, they have not yet achieved an RMP launch.

[62] For further perspective, see Kurata, K. (2009).

The therapy is practiced only within the universities and related clinical organizations, and there is no spread in terms of technology diffusion.

While a certain amount of public funding is invested in clinical research activities and considerable output has resulted, Japan's regulatory system with two pathways is barely effective in leading the output to the commercialization on RMPs' supply and dissemination of regenerative medicine. A valuable opportunity for clinical research is not utilized in launching RMPs. A solution is needed in which the regulatory system works and promotes dissemination of regenerative medicine. The PMDA as a regulatory authority needs to review clinical research as well as clinical trials. To realize this, the two pathways need to be integrated like in other major countries. From the viewpoint of returning output from public funding to the public and improving human welfare, this is an urgent issue.

The regulatory framework for pharmaceutical affairs is a complex system with a variety of factors at play. It will be necessary to increase the number of reviewers in the PMDA if the PMDA is to play a new role of reviewing clinical research. Otherwise, there is the possibility of increased time for market approval, for which the PMDA is criticized even now. The topics discussed in this paper are only part of the complex system, and the discussion is incomplete. Considering the status of introduction of regenerative medicine in Japan and countries such as South Korea, the measures noted in this paper need to be seriously considered as soon as possible.

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