July 29, 2025

WHITE PAPER

Creating a Sustainable Ecosystem for Innovative Regenerative Medical Products

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1. Introduction: Purpose of the Project

Regenerative medical products are products made by processing human or animal cells and tissues for the purpose of reconstructing, repairing and forming body parts, or treating diseases. These products have shown unprecedented treatment results and hold the potential to revolutionize approaches to diseases. In particular, one such regenerative medical product, CAR-T cell therapy, has been approved in Japan, the United States, and Europe as a treatment aimed at achieving a cure with a single administration. It is an industrialized product that has garnered high expectations. CAR-T cell therapy has been put into practical use for treating cancers such as leukemia, lymphoma, and multiple myeloma, showing more significant therapeutic effects than conventional treatments. Its application is now being considered for new disease areas, such as immune and neurological disorders. In addition to the expected clinical value of such therapies, there is anticipation of their social value in reducing medical expenses, including long-term hospitalization and care costs, and in supporting patients' resumption of social and economic activity.

On the other hand, CAR-T cell therapy requires significant investment for research and development, the establishing of a manufacturing and supply system, and the setting up of a medical delivery system before it can be put into practical use. However, there is currently no pricing or reimbursement system that adequately compensates for the complex and advanced processes involved, making it difficult to foresee profits that could be reinvested into new research and development. Additionally, the number of countries and regions capable of manufacturing CAR-T cells is limited, and overall supply is constrained, raising concerns about potential issues such as drug lag and drug loss from the perspective of supply prioritization by pharmaceutical companies.

If the insights and profits gained from treatments cannot be reinvested into the next generation of research and development, the cycle of producing innovative therapies will not continue. For the regenerative medicine and related sectors to keep advancing, it is necessary to build an ecosystem that allows more patients to benefit from innovative treatments and ensures a sustainable and progressive cycle of development. For example, establishing an ecosystem for CAR-T cell therapy, which involves fully individualized production from the patient’s own cells and has a complex development and manufacturing process, could position Japan to take on a leadership role internationally. Moreover, the establishment of such an ecosystem is expected to invigorate the future regenerative medicine industry, bringing significant benefits to patients and their families, to the pharmaceutical industry, and to society as a whole.

To aim for a future where patients with serious medical needs in Japan can continuously receive innovative treatments, it is essential to establish a sustainable ecosystem for regenerative medical products. Additionally, to drive reform, various stakeholders need to come together to engage in discussions from a mid- to long-term perspective. This project aims to take a definitive step forward in these discussions by having experts in medical economics, regenerative medical product technology development, and clinical practice discuss the barriers to the practical implementation of regenerative medical products and the formation of a supporting ecosystem, while exploring solutions from multiple perspectives. Based on the results of these discussions, we plan to identify the issues that need to be addressed in Japan and propose solutions to these.

This white paper is presented by the Japan Research Institute Limited, which aims to contribute to society from a mid- to long-term perspective, and incorporates the viewpoints of public and healthcare professionals, ensuring a fair and impartial perspective.

2. The Need for and Expected Effects of Establishing an Ecosystem for Regenerative Medical Products

2.1. Why Focus on Regenerative Medical Products?

Regenerative medical products are those made by culturing or similar processing through the use of human or animal cells and tissues. They are used for reconstructing, repairing, and forming the structure and functions of the human body, treating and preventing diseases, and for gene therapy.[1] These products offer new treatment possibilities for conditions that are difficult to cure with traditional methods and have the potential to significantly improve patients' quality of life.

The target diseases and forms of regenerative medical products are diverse, and the latter are of high clinical value. They are likely to promote the social reintegration of patients, aid their participation in economic activity, help mitigate the decline in the working population, and support economic stability. Furthermore, regenerative medical products have the potential to significantly reduce the burden not only on patients but also on their families, caregivers, the organizations where patients are employed, and medical institutions. They are seen as contributing to the improvement of overall productivity and sustainable economic growth for society as a whole.

Research and development of regenerative medical products in Japan are steadily progressing with the support of government policies and collaboration between industry and academia.[2,3,4] However, to strengthen competitiveness in the global market, it is urgent to build an ecosystem unique to Japan. In particular, fields such as regenerative medicine, cell therapy, and gene therapy are crucial areas that provide new treatment options for diseases that are difficult to address with traditional therapies. Facilitating the advancement of research, development, manufacturing technology, and market formation in these areas is a critical issue for Japan's healthcare.

2.2. Current Status and Challenges of the Regenerative Medical Products Market

In Japan, laws related to regenerative medicine were established in 2013 & 2014, marking about ten years since their enactment. At that time, technologies related to regenerative medicine were earning a reputation for being innovative, with the potential to lead to early cures for diseases and injuries and aid in the prevention of severe conditions, especially following Professor Shinya Yamanaka's Nobel Prize win in 2012. However, due to the unclear positioning within the regulatory system, there were high expectations for the government's enactment of appropriate laws. The resulting legal framework categorized regenerative medical products under the "Act on Securing Quality, Efficacy, and Safety of Products Including Pharmaceuticals and Medical Devices" (Pharmaceuticals and Medical Devices Act) for insurance-covered medical treatments, and under the "Act on Securing the Safety of Regenerative Medicine" for treatments not covered by insurance and for research purposes, thereby promoting entry and investment along these routes.

However, the anticipated widespread adoption of domestically developed regenerative medicines has not been realized, and it remains a technology handled by a limited number of medical institutions within Japan. Furthermore, the domestic ecosystem is evolving only slowly, and growth rates are not as high as originally envisioned. Under existing rules applying to conventional pharmaceuticals, only two regenerative products had been approved before the establishment of a dedicated regulatory framework, but 20 products have now been approved as of June 2025. However, the market size expected at the time of the legal establishment in 2020[5] has not been reached, and the scale remains small relative to the global market, Japan's share of which is only about 3%. The development of many products approved in Europe and the United States has not progressed in Japan, with fewer than 20% undergoing phase 3 clinical trials.[6] To overcome this stagnation, more aggressive investment in technology development and regulatory reforms are required.

2.3. Government Initiatives for Regenerative Medicine

The Japanese government has undertaken numerous initiatives to promote research and development in the field of regenerative medicines. In addition to the establishment of a regulatory framework in 2013/2014, its "Healthcare and Medical Strategy"[7] was formulated in 2014, clarifying the development of innovative medical technologies, including regenerative medicines, as a national strategy. Further efforts have been made since 2018 to strengthen the support system for the social implementation of regenerative medical technologies through the formulation and revision of the "Integrated Innovation Strategy."[8] At the beginning of the 2020s, the government identified regenerative medicine as a scientific field directly linked to national interests in its "Basic Policy on Economic and Fiscal Management and Reform 2022" and emphasized enhancing the development of regenerative medical products to strengthen drug discovery capabilities in its "Basic Policy 2023." In line with these policies, the government, the Ministry of Economy, Trade and Industry, the Ministry of Health, Labour and Welfare, the Ministry of Education, Culture, Sports, Science and Technology, and the Japan Agency for Medical Research and Development (AMED) have allocated budgets to help fund research and development. Furthermore, the government's "Basic Policy 2024" set forth its commitment to enhancing drug discovery capabilities and promoting healthcare, positioning the development of drugs and regenerative medical products using iPS cells as key measures. Its more recent "Basic Policy 2025" continues this approach, with efforts underway to achieve the early establishment of industrial promotion hubs to lead regenerative medicine production.

Additionally, the "Bioeconomy Strategy"[9] developed by the Healthcare and Medical Strategy Promotion Secretariat sets a goal of global expansion of the market for Japanese-originated regenerative medical products by 2030, aiming at market establishment and industrialization both domestically and internationally. The Ministry of Economy, Trade and Industry is promoting the development of efficient manufacturing processes for regenerative medical products and strengthening domestic industrial infrastructure. The recent "Support Project for Investment in Regenerative, Cellular, and Gene Therapy Manufacturing Facilities"[10] under the FY2024 Supplementary Budget focuses on establishing domestic manufacturing bases for contract development and manufacturing organizations (CDMOs) and developing appropriate human resources to ensure the smooth manufacturing of regenerative medical products and related items in Japan. While current efforts are still in progress, these comprehensive policies are seen as playing a crucial role in building the ecosystem's foundation and enhancing Japan's international competitiveness.

2.4. Necessity of Establishing an Ecosystem for Regenerative Medical Products

Regenerative medical products are groundbreaking technologies that offer innovative treatments, but there are numerous challenges that need to be overcome from the research stage through to actual patient treatment. For example, during the research and development phase, it is necessary to address various issues related to cell and tissue processing. Additionally, it is essential to establish a specialized system for the stable supply of these products, one which requires unique processes such as cell culture and handling. Once a stable supply system is established, these products must undergo evaluation by various regulatory authorities to ensure that they can be provided by medical institutions.

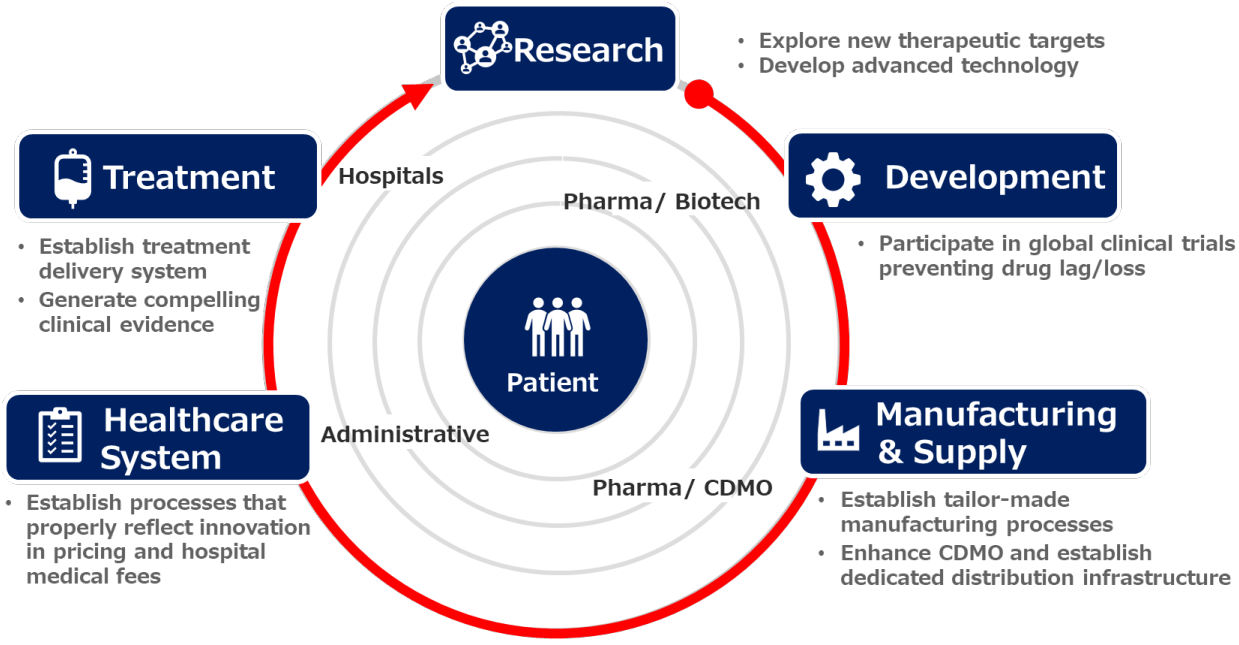

Fig.1 Overview of a sustainable regenerative medicine ecosystem

To sustainably operate this entire process as an "ecosystem," it is essential to reinvest the outcomes from actual clinical practice, as well as the insights and revenue gained, into the research, development, and manufacturing of the next cycle. This enables the development of next-generation products. Ensuring this ecosystem cycle operates sustainably will make it more likely that innovative medical treatments can be delivered to more patients, while simultaneously achieving growth of the sector and advancements in medical care.

2.5. Benefits of Establishing a Regenerative Medical Products Ecosystem

The establishment and continuous proliferation of an ecosystem for regenerative medical products are expected to bring significant benefits to Japan's healthcare industry and to society as a whole, while also enhancing the country’s international competitiveness by demonstrating its leadership in this field.

Producing regenerative medical products domestically for Japanese patients can address global manufacturing and storage limitations, ensuring a sustainable supply. This allows patients to access treatments for severe diseases at an early stage, positively impacting the lives of Japanese patients and their families. It also has the potential to meet future treatment needs for various conditions, such as autoimmune diseases, beyond current levels of demand.

From the perspective of utilizing Japanese talent, building this ecosystem will create opportunities for skilled professionals in research, development, and manufacturing. It can alleviate the burden on healthcare workers, allowing them to focus on treating other diseases, and enable patients who have been cured of severe illnesses—and their families—to become active again, contributing immeasurably to society and the economy.

In terms of international competitiveness, the ability to quickly supply regenerative medical products to Asian countries is crucial. The technology related to regenerative medical products could become the foundation of Japan's bioindustry, accelerating research and development originating from here. This is expected to develop into opportunities for international leadership, expanding Japan's influence in Asia and globally.

[1] Cabinet Bill "Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices."
[2] Cabinet Office Health and Medical Strategy Promotion Headquarters Regenerative/Cell Therapy and Gene Therapy Promotion Council 9th Meeting Document 1-1: Cabinet Office Submission "Government's Overall Efforts in the Field of Regenerative/Cell Therapy and Gene Therapy" (June 2023)
[3] Cabinet Office Health and Medical Strategy Promotion Headquarters Regenerative/Cell Therapy and Gene Therapy Promotion Council "Future Efforts in the Field of Regenerative/Cell Therapy and Gene Therapy" (May 2022)
[4] Cabinet Secretariat "New Capitalism's Grand Design and Execution Plan 2025 Revised Edition" (June 2025)
[5] Ministry of Economy, Trade and Industry, Final Report on the Practical Application and Industrialization of Regenerative Medicine (February 2013)
[6] Ministry of Health, Labour and Welfare, Central Social Insurance Medical Council, Drug Price Special Committee (236th meeting), Statement Materials, The Forum for Innovative Regenerative Medicine "Opinions on the Price Calculation of Regenerative Medical Products" (July 2025)
[7] Healthcare and Medical Strategy (Cabinet decision, July 2014), etc.
[8] Integrated Innovation Strategy (Cabinet decision, June 2018), etc.
[9] Bioeconomy Strategy (Integrated Innovation Strategy Promotion Council decision, June 2024)
[10] Ministry of Economy, Trade and Industry, FY2024 Supplementary Budget "Support Project for Investment in Regenerative, Cellular, and Gene Therapy Manufacturing Facilities"

3. Clinical and Social Value of CAR-T Cell Therapy

3.1. Overview of CAR-T Cell Therapy

This white paper focuses on CAR-T cell therapy and identifies specific challenges involved in the delivery of regenerative medical products. The reasons for this focus include the significant clinical and societal value of CAR-T cell therapy, the complexity of its manufacturing and quality control process, given that it's a personalized medicine, and its approval and industrialization in Japan, the U.S., and Europe alongside other regenerative medical products.

CAR-T cell therapy involves harvesting a patient's T-cells, reprogramming them using gene-editing technology to specifically recognize and attack cancer cells, and then expanding these cells and administering them back into the patient as a regenerative medical product. This innovative, fully personalized medical treatment is currently approved in Japan for five products that treat hematologic cancers such as B-cell acute lymphoblastic leukemia, large B-cell lymphoma, and multiple myeloma. Additionally, CAR-T cell therapy shows potential efficacy for solid tumors and autoimmune diseases, suggesting its potential for broader disease applicability.

3.2. Clinical Value of CAR-T Cell Therapy

The clinical value of CAR-T cell therapy is assessed based on the outcome of clinical trials and on post-marketing clinical data. This treatment aims to provide a cure for severe diseases and can achieve long-term remission. Clinical trial results indicate groundbreaking effects on overall survival (OS) and quality-adjusted life years (QALY) with a single administration for patients with severe hematological cancers.[11,12] High response rates and survival have also been reported in post-marketing clinical trials.[13] Furthermore, CAR-T cell therapy has an established safety profile,[14] it has significantly improved patient outcomes in cases of diseases that were previously challenging to treat, and as an innovative therapeutic has expanded treatment options. The clinical value is validated by real-world data,[15] suggesting a transformative impact on cancer treatment and potential application across a wide range of diseases.

3.3. Societal Value of CAR-T Cell Therapy

As a one-time personalized therapy, CAR-T cell therapy reduces the need for long-term treatment involving regular hospital visits, administration, and ongoing costs, improving patients' long-term quality of life (QoL). Improved health leads to early social and economic reintegration for patients, enhancing productivity and reducing the burden on families and caregivers.

From an economic standpoint, CAR-T cell therapy is of high societal value. For instance, U.S. estimates suggest a 30.3% cost reduction using cell therapy to treat multiple myeloma compared to standard treatments. This is attributed to a reduction in ongoing chemotherapy costs, hospitalization days, and outpatient visits; it also reflects a reduction in the loss of overall lifetime earnings for patients and of caregiver productivity.[16] Additionally, efficient resource allocation by organizations and medical institutions helps ensure sustainable healthcare, enhancing access to quality treatments for more patients.

Given Japan's declining labor force and increasing individual economic value, CAR-T cell therapy is expected to significantly impact positively on a broad spectrum of society. As an important medical innovation, further dissemination of CAR-T cell therapy is anticipated.

[11] Bristol Myers Squibb, "TRANSCEND trial: Largest pivotal trial in 3L+ large B-cell lymphoma, including patients with high-risk disease."

[12] Gilead Sciences, "Yescarta® Is First CAR T-cell Therapy to Report Five-Year Survival Data From Pivotal Study Showing Durable Long-Term Survival in Patients With Refractory Large B-cell Lymphoma" (December 2021).

[13] Neelapu SS. Five-year follow-up of ZUMA-1 supports the curative potential of axicabtagene ciloleucel in refractory large B-cell lymphoma. Blood. 2023;141(19):2307-2315.

[14] Abramson JS. Lisocabtagene maraleucel as second-line therapy for large B-cell lymphoma: primary analysis of the phase 3 TRANSFORM study. Blood. 2023;141(14):1675-1684.

[15] Crombie N. Real-world outcomes with novel therapies in R/R DLBCL. Hematol Oncol. 2023;41(3):453-468.

[16] Alliance for Regenerative Medicine, "A Transformative Therapy Value Model for Rare Blood Diseases" (January 2020).

4. Challenges and Opportunities in the Development and Manufacturing of CAR-T Cell Therapy

The manufacturing of regenerative medical products involves a process distinct from that of traditional pharmaceuticals, necessitating a specialized framework. Due to the personalized nature of these treatments, standardizing quality control and production processes poses a challenge. Recently, under the leadership of the Ministry of Economy, Trade and Industry, efforts to establish manufacturing infrastructure have been making steady progress. However, further improvements in manufacturing technology and cost reduction are essential to create a system that can deliver treatment to more patients.

On the supply side, it is crucial to enhance collaboration with medical institutions and optimize the supply network to ensure that patients requiring treatment can access regenerative medical products at the right time. Specifically, establishing a distribution system to ensure a stable supply of products is vital.

4.1. Manufacturing and Supply Process of CAR-T Cell Therapy

CAR-T cell therapy is a fully personalized treatment produced by genetically modifying a patient's own T-cells, and involves a complex manufacturing and supply process. Initially, T-cells are extracted from the patient using leukapheresis and transported to a pharmaceutical company's cell processing facility. There, genetic modification techniques are used to introduce chimeric antigen receptors (CARs) into the T-cells, enabling them to specifically recognize and attack cancer cells. The genetically modified T-cells are then expanded in a culture environment. Throughout this process, quality control tests are conducted to ensure only qualified cells are frozen and shipped as products. These are then transported to treatment facilities, thawed, and administered to the patient under strict side-effect management protocols.

4.2. Challenges in the Development, Manufacturing, and Supply of CAR-T Cell Therapy

While CAR-T cell therapy is innovative compared to traditional pharmaceuticals, it faces numerous challenges in its development, manufacturing, and supply processes. Traditional pharmaceuticals can be mass-produced uniformly through chemical synthesis or large-scale cultivation, and efficiently supplied to a large number of patients by maintaining inventory and utilizing logistics networks. In contrast, CAR-T cell therapy involves handling living cells derived from the patient, requiring specialized facilities and equipment. The manufacturing and quality control processes rely heavily on personalized tasks carried out by highly specialized and trained personnel. Furthermore, the technologies are covered by numerous patents, leading to high licensing fees. The therapy also involves expensive, specialized raw materials, some of which face supply shortages, driving up prices. Transportation requires dedicated logistics, including specific packaging and infrastructure (such as cold supply chains that maintain temperatures of minus 150°C), necessitating transport from medical facilities to cell processing facilities and back for each patient. Currently, CAR-T cell therapies are primarily manufactured overseas, with transport complexities and time lags posing unique challenges.

CAR-T cell therapy, being a fully personalized treatment, incurs high production costs, R&D expenses, and distribution costs, unlike traditional pharmaceuticals where economies of scale apply. Moreover, since the manufacturing process significantly impacts the efficacy and quality of the final product, integrating commercial perspectives into the development process from an early stage is crucial. Internationally, a startup ecosystem allows biotech startups to commercialize academic seeds and secure funding from venture capital and investment markets. Leveraging this financial strength, pharmaceutical companies and CDMOs get involved early, accelerating development. In contrast, Japan's startup ecosystem is underdeveloped, and the current pricing structure makes the domestic market less attractive compared to other countries. Consequently, attracting investment to finance the conducting of clinical trials and manufacturing in Japan is challenging, delaying the shift towards a commercially-driven manufacturing process and, consequently, practical application.

Overcoming these challenges requires technological innovation and an expansion of manufacturing scale. Standardizing and streamlining manufacturing technologies, optimizing supply chains, developing highly specialized human resources, and establishing facilities are imperative. By achieving this, Japan will undoubtedly enhance its international competitiveness.

4.3. Opportunities in the Development, Manufacturing, and Supply of CAR-T Cell Therapy

Conversely, the development, manufacturing, and supply of CAR-T cell therapy present significant opportunities for Japan. Currently, few countries offer CAR-T cell therapy, and Japan has the potential to lead globally in manufacturing, clinical development, and evidence generation. Through initiatives like the Ministry of Economy, Trade and Industry's "Regenerative Medicine Industrialization Infrastructure Program," the Japanese government is actively investing in the establishment of manufacturing facilities and CDMOs for regenerative-, cell-, and gene therapies, including CAR-T cell therapy. These initiatives aim to strengthen domestic manufacturing capacity, position Japan as a hub for manufacturing and supply in Asia, and enhance the country's international competitiveness.

Government policies are expected to promote the development of specialized human resources and the establishment of facilities, providing a foundation for advancing supply chain sophistication. This will enable Japan to demonstrate leadership in this field, offering treatment access to a wider range of patients and creating opportunities for new treatments.

5. Challenges in the Medical Insurance System and Provision of CAR-T Cell Therapy

Japan's healthcare insurance system operates under a universal health coverage framework, enabling relatively swift reimbursement after approval.[17] Additionally, advanced medical facilities utilizing regenerative medical products are available nationwide, providing an environment conducive to patients receiving cutting-edge treatments. To offer regenerative medical products as a treatment option for a wide range of diseases, it is crucial to establish a system that ensures sustainable provision through the insurance reimbursement system. However, the pricing of products, reimbursement as medical technology, and investments in medical facility infrastructure are designed as extensions of traditional systems, and it is difficult to say that the unique characteristics of regenerative medicine have been fully assessed. In particular, discussions are needed on how to reflect in the insurance reimbursement system the long-term outcomes for patients, the reduction of burden on caregivers, and the contribution to society that regenerative medical products can offer. Consideration is also needed of how to align with the current system, given that economies of scale based on manufacturing volumes do not fully apply, and how to target investments in medical institutions in such a way that innovative treatments will be disseminated.

5.1. Challenges in Pricing and Repricing Systems

In Japan, keeping prices low facilitates quick and widespread insurance reimbursement. In contrast, in Europe, companies tend to set higher prices, with reimbursement often delayed due to cost-effectiveness evaluations. However, setting prices too low may reduce incentives for companies to engage in research and development, potentially leading to drug lags or losses. In Japan, product prices tend to be lower than in other countries. Although the number of approved CAR-T products is not large in Japan and other countries, a 2023 survey comparing CAR-T cell therapy product prices showed that each product cost approximately 33 million yen in Japan. In contrast, prices ranged from 68 million to 87 million yen in the U.S., 45 million to 46 million yen in the UK, 37 million to 59 million yen in Germany, and 37 million to 59 million yen in France.[18] The insurance-listed price in Japan for the allogeneic mesenchymal stem cell product Alofisel for the treatment of complex fistulas in Crohn's disease was about 5.6 million yen, compared to about 6.9 million yen in France.[19] For the gene therapy Zolgensma used to treat spinal muscular atrophy, the price in Japan was approximately 167 million yen, compared to 230-280 million yen in the U.S.[20] Meanwhile, Luxturna, approved for hereditary retinal dystrophy, was priced at about 50 million yen in Japan, roughly equivalent to the UK price and higher than France's price of about 41 million yen.[21] However, the peak number of patients was five, suggesting minimal impact on healthcare finances. Currently, with the weakened yen, overseas prices denominated in yen have risen further, widening the gap with Japanese prices.

Additionally, while prices rarely increase post-reimbursement in Japan, overseas systems that allow for price increases contribute to further widening the gap.

5.1.1. Long-term Clinical and Societal Value

Japan's national medical expenses amounted to 46.6967 trillion yen in the fiscal year 2022 [22] and are expected to approach around 50 trillion yen by the fiscal year 2025, driven by increasing medical demand resulting from the country's declining birthrate and aging population. In response to concerns about rapidly increasing financial burdens, the government has repeatedly sought to contain unit costs and quantities through measures such as medical fees and product pricing, which may put further pressure the revenues of healthcare institutions, pharmaceutical companies, and related industries. Against this backdrop, companies face profitability challenges, healthcare institutions face issues with facilities, equipment, and human resources, and patients face the risk of drug lags and losses. Moreover, a significant concern is the inability to reinvest profits derived from innovations into next-generation development.

As a fundamental reform proposal to address these issues, the following two points have been suggested and discussed by the Institute for New Era Strategy.[23] It is considered necessary to design a system with a view toward the medium- to long-term future.

a. Management of Total Healthcare Expenditure in Line with Economic Growth

Discussions are underway on managing healthcare expenditure to a certain extent to prevent excessive healthcare cost containment from adversely affecting patient health and the quality of care. For example, one proposal suggests managing the pharmaceutical cost portion of healthcare expenditure so that it grows in line with the long-term nominal GDP growth rate. By numerically indicating the upper and lower limits of the funding framework in advance, the proposal aims to create a highly predictable environment that prevents sudden and mechanical price reductions while ensuring appropriate resource allocation to innovative pharmaceuticals. Notably, nominal GDP growth includes the GDP deflator, allowing for appropriate reflection of price-related growth in pharmaceutical costs.

b. Introduction of a System to Evaluate Diverse Values

To balance improving healthcare quality and sustainability, discussions are underway on improving the opaque process of health technology assessment, which currently focuses primarily on cost and QALY (Quality-Adjusted Life Years). Proposals include a fundamental improvement to value assessment by incorporating comprehensive value elements (the impact on work, the health of caregivers and families, societal impact) while defining and classifying pharmaceuticals and technologies with clinical effects and social benefits below a

certain standard as low-value healthcare. Gradual reductions in insurance points and exits from reimbursement are being suggested, along with the presentation of alternative treatments.

Regarding the adjustment premiums in pricing, regenerative medical products require long-term observation of outcomes post-transplantation or administration, and it's often the case that all required items are not thoroughly verified at the time of application. Moreover, regenerative medical products offer contributions that are not fully captured by the current adjustment premiums. A significant challenge for Japan is the projected increase in overall medical demand and per capita healthcare costs due to the aging population as the country heads toward 2040, leading to increased burdens on the working population. Regenerative medical products are particularly capable of addressing this challenge by offering potential treatments or cures for diseases that are difficult to resolve with conventional medical technologies, thus potentially reducing long-term hospitalization and caregiving costs and improving productivity through the reintegration of workers into society. In fact, when the cost-effectiveness of Kymriah was evaluated, estimations of productivity loss, though preliminary, yielded positive results.[24]

To establish a foundation for data collection and analysis in real-world clinical settings and promote reverse translational research that feeds back clinical insights and challenges into next-generation R&D, it is necessary to give greater consideration to a premium system where innovations, once their post-market efficacy and safety are verified, are adequately reflected in the pricing of existing products.

The perception of value in healthcare varies depending on the recipient, and certain aspects of this may lead to conflicts of interest among stakeholders. However, a proposal for a system design that allows the value provided by regenerative medical products to be presented with evidence data by companies and academic societies, and reflected as adjustment premiums when socially recognized, would be beneficial for the future of our country.

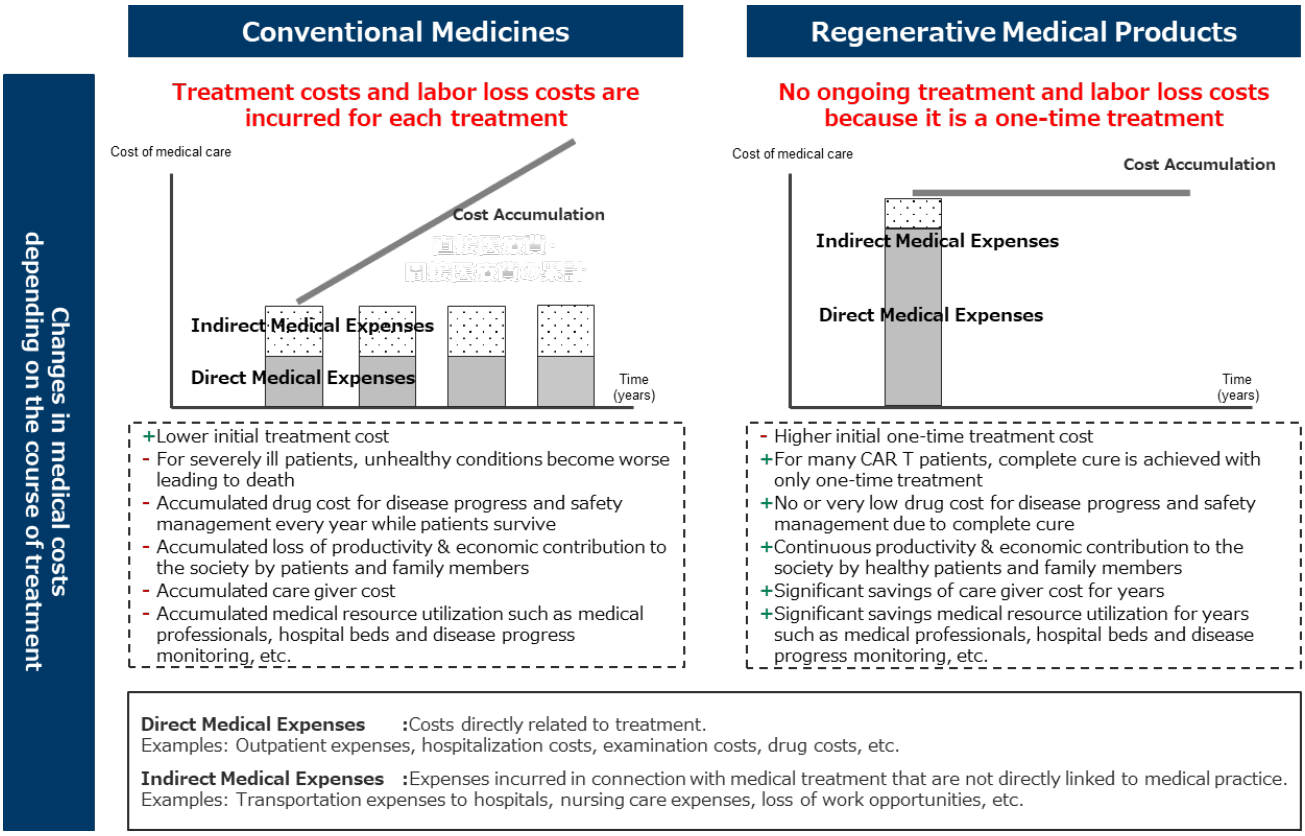

Figure 1Trends in costs of conventional pharmaceuticals and regenerative medicine products

5.1.2. Lack of Economies of Scale due to Personalized Manufacturing

Japan's drug pricing system includes mechanisms that can uniformly lower the price of innovative drugs even during their patent period, one of which is called “market expansion repricing.” The market expansion repricing system is designed to optimize healthcare costs and efficiently manage budgets by reevaluating the price of a drug if its market size significantly exceeds initial projections. The specific criteria for this system are as follows:

- ✓ If the market size is more than double the initial forecast and annual sales exceed 15 billion yen.
- ✓ If the drug has not undergone cost-based price revisions and the market size is ten times the initial forecast, with annual sales exceeding 10 billion yen.

This system operates on the premise that economies of scale can reduce the per-unit cost of drugs that can be mass-produced. However, CAR-T cell therapies require complex and personalized manufacturing processes that incur high costs for specialized personnel development, quality control, logistics, and post-manufacturing operations. Even if the number of patients supplied increases, production remains individualized, necessitating an expansion of

transport and supply lines, making cost reduction through mass production impossible. Additionally, global manufacturing and supply are limited, and if prices are suppressed due to Japan's pricing system or currency exchange rates, it could become challenging to maintain patients' access to the treatment due to prioritization decisions, potentially limiting treatment options.

Currently, CAR-T cell therapy products are not subject to market expansion repricing or "yoking," but with an increase in the number of eligible patients, they may become subject to these in the near future. To ensure a sustainable supply for Japanese patients, it is reasonable to consider revising the market expansion repricing system.

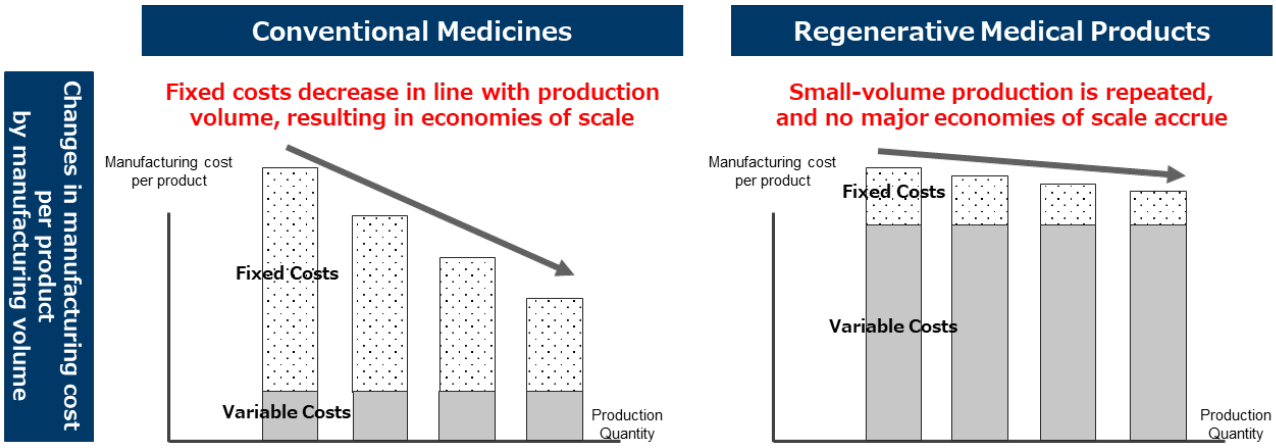

Figure 2Relationship between product manufacturing costs and production quantity of conventional pharmaceuticals and regenerative medicine products

5.2. Challenges in the Medical Fee System

To promote the widespread use of regenerative medical products, it is essential to establish a system that allows medical institutions to actively invest in infrastructure and human resource development while ensuring their profitability. Currently, there are challenges in building a framework that enables medical institutions to provide high-quality healthcare sustainably. Specifically, the setting of appropriate fees for procedures and management to enhance facility investment and human resources is inadequate, making it difficult for medical institutions to realize a profit. For instance, the reimbursement for CAR-T cell therapy procedures is currently based on the system for autologous peripheral blood stem cell transplantation, which has a similar process. However, the costs associated with the medical delivery system, such as necessary personnel and equipment, are not fully covered by the existing reimbursement. Notably, only one apheresis is reimbursed per CAR-T cell production, and if the first apheresis does not meet the standards and must be repeated, it is not covered, becoming a financial burden for the medical institution.[25] Additionally, the transportation and reception of cells to and from manufacturing facilities and the preparation of ultra-low temperature transport containers are necessary, but the cost of these is not reimbursed. Furthermore, CAR-T cell therapy requires much more sophisticated and prolonged side-effect management compared to autologous peripheral blood stem cell transplantation, and this is not adequately considered in terms of management and medication.

When designing the reimbursement system, it is necessary to create a framework allowing medical institutions to proactively invest in infrastructure and human resource development while generating a profit. Addressing these challenges will improve the quality and accessibility of regenerative medical healthcare and enable the sustainable development of appropriate products.

5.3. Challenges in Patient Access to Treatment

Ensuring patient access to regenerative medical products and creating an environment where they can receive treatment with confidence requires the following challenges to be overcome:

5.3.1. Diagnosis to Initial Treatment and Relapse Process

Patients experience significant changes in their daily lives and feel anxiety about the disease's progression and prognosis throughout the process from diagnosis to initial treatment and relapse. Additionally, due to a lack of understanding of the disease itself and of information on treatment options, including regenerative medical products, patients find it difficult to determine how best to proceed. Moreover, concerns that they may have to move from hospital to hospital

and worries over the side-effects of treatments are significant deterrents to undergoing treatment.

5.3.2. Access to CAR-T Cell Therapy

In clinical trials of CAR-T cell therapy, specific serious adverse events, such as cytokine release syndrome, have been reported. Due to safety considerations, treatment is only allowed at specific eligible facilities. However, the number of facilities in Japan able to provide this treatment varies by product, ranging from 36 to 67 facilities,[26] making access particularly difficult for patients living in rural areas. In the U.S., CAR-T cell therapy's status as a treatment option is well-established in clinical guidelines.[27] By contrast, in Japan it is merely listed as one of many treatment options,[28] influencing treatment choices by patients and physicians. Furthermore, there is no effective system or network to link treatment-providing facilities with referral facilities, nor are there specialized coordinators, leading to a burden in providing medical information and insufficient incentives for patient referrals. Consequently, access to appropriate treatments for patients needing regenerative medical products is limited. This is especially problematic in the case of acute diseases, where there is often a lack of smooth communication and prior discussions about subsequent treatments, such as CAR-T cell therapy, between patients and referring physicians prior to relapse.

5.3.3. From Treatment to Follow-up

Patients continue to experience significant anxiety from treatment through follow-up. Particularly, concerns about the latter are substantial; better follow-up mechanisms are needed to allow patients to handle their prognosis with confidence.

5.3.4. [Note 1] Summary of discussions regarding the use of private insurance

In Japan, the constantly increasing cost of healthcare is giving rise to concerns about the sustainability of the public health insurance system. Proposals are being considered to exclude some high-cost medications from public insurance coverage and to utilize private insurance to help contain social insurance premiums. The public health insurance system aims to achieve its ideal of Universal Health Coverage, ensuring that, when facing significant risks, everyone can access the medical services they need without any financial worries. However, excluding expensive medications from public insurance coverage could pose a serious challenge to this ideal. Additionally, as medical technology advances and treatment options diversify, restricting these options due to financial reasons would be counterproductive to improving the quality and accessibility of healthcare. From this perspective, it is desirable that regenerative medical products and related technologies continue to be covered by the public health insurance system.

On the other hand, the government plans to expand the scope of treatments that can be used alongside those covered by insurance, specifically targeting cutting-edge medical technologies whose effectiveness is not yet fully validated, as opposed to officially approved products like CAR-T cell therapies.[29] Currently, the insights gained from the use of regenerative medicine as a medical technology under safety assurance laws are not fully utilized in the formulation of the next-generation ecosystem. Moving forward, it is necessary to implement measures that reflect these insights in the research and development of next-generation treatments through proactive reverse translational research. For example, research and treatment plans aimed at acquiring evidence, such as advanced medical care or patient-requested therapies, should be made available to those covered by public health insurance, to reduce the burden on patients, encourage public participation, accumulate case numbers, and improve the quality of research and treatment. Additionally, supporting these systems requires collaboration with private insurance providers. For private insurance providers to cover a specific condition and for coverage to become established and flourish, they must assume a lower disease risk, with a large potential market size and a broad segment of the population facing the risk. In areas meeting these conditions, it would be beneficial to consider the development and utilization of private insurance to help alleviate individual burdens.

5.3.5. **[Note 2] Cost-Effectiveness Evaluation System**

The “Basic Policy on Economic and Fiscal Management and Reform 2025” (“Honebuto no Hoshin 2025”) [30] states:

“Based on objective verification, further utilization of the cost-effectiveness evaluation system will be considered, including appropriate evaluation methods, the scope of application, and the implementation structure, as well as its use in the drug pricing system and clinical practice.”

This indicates a direction toward expanded application of the system in the future.

Analyzing the European HTA landscape, 'cost-effectiveness evaluation,' or 'economic HTA,' is not applied to regenerative medical products in key reference countries like Germany and France. The primary reason for this is that standard economic HTA lacks the flexibility to account for broader considerations, such as long-term economic and scientific values. Applying standard economic HTA could lead to significant drug lag and loss for regenerative medical products.[31]

While economic HTA is not undertaken in countries like Germany and France, clinical HTA focuses on clinical value assessment, including patient-reported outcomes (PRO). However, regenerative medical products are highly complex, with challenges in blinding, randomization, endpoint selection, and choice of comparator, which results in uncertain evidence regarding their long-term value at the time of regulatory submission. Even clinical HTA has limitations in fully capturing the long-term, potentially lifetime, benefits of regenerative medicine products.

However, for example, in Sweden, economic HTA is applied to with greater flexibility which helps regenerative medical products. They incorporate flexible thresholds for the Incremental Cost-Effectiveness Ratio (ICER), Quality-Adjusted Life Years (QALY), cost-benefit analysis, and budget impact to enable faster patient access to life-saving regenerative medical products. Sweden’s HTA system also systematically includes ‘Indirect costs and benefits’, which supports their access as regenerative medical products have a positive impact on this domain of HTA.

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5.3.6. [Note 3] Price Stability and Manufacturing Incentives to Promote Innovation and Investment in France

In France, a framework agreement between LEEM (The French Pharmaceutical Companies Association) and CEPS (The Economic Committee for Health Products) has established a system providing price stability and manufacturing incentives (currently under renegotiation). It incorporates incentives designed to promote domestic manufacturing, support exports, by ensuring that prices for highly innovative medicines do not fall below those in other European countries.[32]

They include the following:

- To promote domestic manufacturing of innovative medicines, for products rated ASMR 1–3 (indicating high added clinical value compared to existing therapies), if all major manufacturing steps are conducted in France, the price must not be lower than the lowest price in either the UK, Germany, Italy, or Spain.
- If current or future investments in manufacturing, R&D, or digital health related to the product are made within the EU—particularly in France—up to five years of price stability may be granted.
- To encourage exports, products for which at least one significant manufacturing step is conducted in the EU (especially in France), batch release is performed in France, and more than 60% of production volume is exported, may be granted two years of price stability (renewable once for up to two additional years).
- For many innovative medicines rated ASMR 1–3, if the price is set by referencing other European countries and the health economic assessment is valid, net and list price stability is granted for the first five years after market launch (three years in other cases).

In Japan, similar incentives may be necessary to promote the R&D and manufacturing of regenerative medicine and related products, and to support their development as an export industry. Specifically, ensuring that domestic prices do not fall below referenced European prices could be a key policy consideration.

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6. Actions and Policies Necessary for the Dissemination and Sustainability of Regenerative Medical Products

Efforts to establish a regenerative medical product ecosystem are being propelled somewhat by government initiatives at various stages, including research, development, manufacturing, and supply. However, there remains a lack of a comprehensive system in terms of healthcare insurance and the establishment of a treatment-providing framework, indicating that the current ecosystem is insufficient for seamless operation.

Recommendation 1:

Reform of the pricing system and medical fee system to promote the spread of regenerative medical products

Japan's healthcare insurance system operates on a principle of universal health coverage, providing an environment conducive to receiving advanced treatments. By keeping prices low, Japan facilitates rapid and extensive insurance reimbursement, whereas in Europe, high pricing set by companies often results in delayed reimbursement due to cost-effectiveness evaluations. However, setting prices too low could reduce the incentive for companies to invest in research and development, potentially leading to drug lags or losses. Implementing systemic reforms that reflect the innovation and characteristics of regenerative medical products could position Japan as a global leader in this field, thereby delivering the benefits of treatment to more patients.

Ensuring sustainable access to regenerative medical products requires comprehensive reform of the healthcare insurance system. First, it is necessary to review pricing to properly assess innovation and reconsider market expansion repricing. Additionally, in order to utilize limited medical resources efficiently, strategies to reduce medical costs, such as curbing excessive medication usage and ensuring appropriate use, should also be considered.

- **Adequate reflection of the usability rating in the price**

Regenerative medical products not only offer clinical value over long periods but are also a benefit to society by aiding patient reintegration into society and reducing the burden on caregivers. It is important to consider how these contributions over an extended timeframe can be reflected in the form of adjustments to premiums within the healthcare insurance system. Furthermore, using this system as an incentive, it is necessary to promote the collection and analysis of real-world clinical data and reverse translational research for verification.

- **Revision of the application of the market expansion repricing**

Regenerative medical products undergo complex manufacturing and distribution processes, incurring significant costs in terms of specialized facilities, personnel, intellectual property, special quality control, and post-production operations. Additionally, these products are individually manufactured for each patient, lacking economies of scale, and making cost reduction through mass production difficult. Applying market expansion repricing, which assumes economies of scale, could severely impact company revenues and hinder continued patient access. Therefore, reviewing current market expansion repricing rules, which assume economies of scale for conventional pharmaceuticals, is necessary. At the very least, establishing a mechanism that prevents excessive price reductions during scope expansions would help maintain an environment where companies can supply innovative treatments in a sustainable manner.

- **Improvement of the medical fee system to properly reflect medical costs**

To enable the sustainable provision of regenerative medical products, support for facility investment and human resource development at medical institutions is crucial. Thus, when setting reimbursement rates, it is necessary to evaluate the costs of medical provision systems, including the personnel and facilities required for the provision of regenerative medical products, sufficiently within reimbursement rates. Additionally, it is important to incorporate systems that allow medical institutions to recoup their investment in facilities and personnel.

Recommendation 2:

Review Ecosystem Challenges and Continue with Policies that will Enhance Next-Generation Cycles

To develop an ecosystem for regenerative medical products, it is essential to make ongoing efforts to identify challenges, improve processes, and refine these; this will help enhance the next generation of medical technologies. While the government currently supports the establishment of research, development, manufacturing, and supply systems for regenerative medical products, transient investments alone cannot sustain the ecosystem. To ensure Japan becomes a more attractive market, it is essential to balance regulatory system enhancement, reinvestment of profits gained from initial cycles by private companies, and the further expansion of government investment funds from a bio-industry development perspective.

- **Promote measures to strengthen stakeholder collaboration**

In innovative technology development, it is crucial to swiftly and efficiently introduce research findings to the market. Bridging research plays a vital role in this process. The government and relevant ministries should promote policies that facilitate the transfer of university-originated technologies to startups and push rapid product development.

To ensure smoother provision of regenerative medical products, it is urgent to build systems and strengthen networks in order to link referring facilities with treatment-providing facilities more effectively. By enhancing collaboration among medical institutions, clarifying the positioning of regenerative medical products in clinical guidelines, and boosting incentives for patient referrals, a network should be developed to ensure that patients requiring regenerative medical products receive treatment quickly and appropriately.

To improve patient awareness and ensure their access to treatment, patient organizations, academic societies, medical institutions, and development companies need to collaborate in building forums for sharing and discussing the latest information on diseases and the various treatment options, including immunotherapy, and create comprehensive and easy-to-understand guidance.

Furthermore, evidence derived from real-world clinical data should be accumulated and fed back into next-generation research and development. With the participation of treatment-providing facilities, academia, development companies, and patients, it is important to verify the long-term value of regenerative medical products and build the kind of foundations that will help ensure their further development.

● Continue to reduce costs and develop infrastructure

The manufacturing, quality control, and supply of regenerative medical products remain in the early stages of refinement, with many processes relying on manual labor by highly skilled personnel, resulting in high manufacturing costs. However, with technological advancements such as automation and robotics, future cost reductions are anticipated, allowing more patients to benefit from new regenerative medical treatment opportunities across various diseases.

The government should aim to nurture highly specialized human resources, promote facility development, enhance supply chains, and establish a domestic ecosystem, solidifying Japan's position as a base for expansion into Asian countries.

WHITE PAPER
Creating a Sustainable Ecosystem for Innovative Regenerative Medical Products
July 29, 2025

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[Sponsor]
Bristol-Myers Squibb K.K.

This white paper proposal was created with the sponsorship of Bristol-Myers Squibb.