Consideration of and expectations for the Pharmaceuticals, Medical Devices and Other Therapeutic Products Act in Japan

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1. Introduction

Regenerative medicine is a method to treat diseased or damaged organs using stem or somatic cells and tissues. The method enables the treatment of intractable diseases or injuries, and efforts to develop innovative techniques of regenerative medicine have increased considerably in recent years [1]. Since 2011, the regulatory frameworks for pharmaceuticals and medical devices in Japan have been reexamined and the revised Pharmaceutical Affairs Law, which was renamed the Pharmaceuticals, Medical Devices and Other Therapeutic Products Act (PMD Act), was developed in 2013 and implemented in November 2014 [2,3]. Based on this new legal framework, Japan will have the potential to become a prime venue for international medical researchers and industries [4]. This article aims to examine how this framework could be utilized as an appropriate system to develop innovative regenerative medicine.

1.1. The new framework for regenerative medical products and the PMD Act

The field of regenerative medicine using regenerative medical products has become a major focus of global research. Regenerative medicine aims to regain the function of organs damaged by illness or injury and increases the possibility of finding a treatment for intractable diseases. Therefore, promoting regenerative medicine can be expected to become a new focus for patients who suffer from incurable diseases and injuries. However, because regenerative medicine utilizes ingredients derived from living cells and tissues, it carries a risk of bacterial or viral infection and tumorigenicity. It is therefore imperative that sufficient safety measures are established in parallel with the promotion of regenerative medicine.
emergency economic policy measures (January 11, 2013; Japanese Cabinet Decision), the reexamination of a special expedited reviewing system for regenerative medical products was initiated. In parallel with this emergency policy, the Regenerative Medicine Promoting (RMP) Act was established. This Act defines the responsibilities of the government and citizens in Japan to utilize regenerative medicine, and a scheme to enable the rapid and safe clinical application of regenerative medicine was enacted by the Diet, the national legislature of Japan, on April 26, 2013 [5]. The RMP Act aims to comprehensively promote the use of regenerative medicine by ensuring its safety. Following the introduction of this Act, the government submitted the PMD Act, which is the revised version of the Pharmaceutical Affairs Law [2,6].

As the first change to the PMD Act, regenerative medical products related to regenerative medicine or gene therapy were newly defined. Regenerative medical products fall into two groups: (1) products processed from the cells of a human or animal, with the purpose to reconstruct, repair, or reform the physical structure of a human or animal, or to treat or prevent the disease of a human or animal, and (2) products that are introduced into the cells of a human or animal to promote the development of a gene in the body to treat illness of a human or animal. In addition, the Government Ordinance of the PMD Act lists the categories of the products [7]. Human cell processing products include the following: (1) human somatic cell processing products, (2) human somatic stem cell processing products, (3) human embryonic stem cell processing products, and (4) human artificial pluripotent cell processing products. Gene therapy products include the following: (1) products derived from plasmid vectors, (2) products derived from virus vectors, and (3) gene expression treatment products (quality to advocate to previous two is excluded). Furthermore, in Notice no. 5 issued by the Director for Medical Devices and Regenerative Products Review, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare (MHLW; August 12, 2014) [8], “processing” is defined as the artificial expansion/differentiation of cells, establishment of a cell line, chemical treatment to activate cells or tissues, modification of biological characteristics, combination with non-cell/tissue components, and genetic modification of cells, cells for non-homologous use, all of which are conducted for the purpose of treatment of diseases, or the repair or reconstruction of tissues. “Processing” does not include the following operations: separation and cutting of tissues, isolation of specific cells (except for isolation following biological/chemical treatments), treatment with antibiotics, washing, sterilization by gamma ray, freezing, thawing (but not using cells for the purpose intended to gain different structure and function from their original cells). Examples of products that are not considered as regenerative medical products include human red blood cell, human platelets, fresh frozen plasma, blood plasma fractions, hematopoietic stem cells grafts, fertilized embryos and gametes for reproduction assistance medical care, placental extract (placental tissue), human amnion, human endocardium, bioprosthetic valves, high mud gel for wounds, dental plates, bone cement, artificial joints, artificial vessels, cell stock solutions, attenuated live vaccines published by a Standard of Biological Products [9], antisense oligonucleotides, nucleic acid derivatives, ribozymes, and aptamers.

The second major change to the PMD Act is described below. Because regenerative medical products use human/animal living cells, which have heterogeneous qualities, long periods of time are required to collect data and evaluate the effectiveness of treatment. Therefore, a conditional/time-limited approval system was established to facilitate the early clinical application of regenerative medical products. This system enables the effectiveness of products to be estimated early based on constant updates from the limited numbers of cases treated. Acute side effects can be identified from short-term investigations, and the long-term safety is evaluated in the post-marketing surveillance of a registry of all patients, which is scheduled to be in place in 2015. The registry of all patients treated with regenerative medical products is to be initially controlled by the Pharmaceuticals and Medical Devices Agency (PMDA), which is supported by the MHLW.

To further ensure the maintenance of safety measures, it is clearly stated that doctors should provide patients with a thorough explanation of all procedures and should obtain prior informed consent. Doctors are also obliged to keep complete records on the use of regenerative medical products. In addition, regenerative medical products are to be included under the umbrella of the Relief Services for Adverse Health Effects.

A further revision was the generation of a new standard (Good, Gene, Cellular and Tissue-based Products Manufacturing Practice; GCTP) for manufacturing management and quality control in the industry to secure the quality and safety of the products [10]. In addition, while it was previously forbidden to collect blood from humans for manufacturing products other than blood and plasma products, the new Act enables industry or hospitals to produce regenerative medical products using blood collected from humans as an ingredient.

1.2. New points for consideration in developing regenerative medical products

For the appropriate development of regenerative medical products, it is important to consider quality, safety, and efficacy. First, the following points should be considered to evaluate the quality of the products [11]. The management of ingredients must be appropriate, and the quality of the ingredients must meet the Minimum Requirements for Biological Ingredients [12]. However, it may be difficult to determine whether the characteristic analysis of a product is sufficient. For example, it is important to ensure that there has been appropriate confirmation and quantitative evaluation of selected or rejected cells, that eligibility tests of selected cells have been conducted, that the proliferation properties of cells are determined, and that the kind and quantity of impurities derived from the process of manufacture are reasonable. In addition, for regulatory inspection, process validation/verification during the manufacturing process and quality control should be performed appropriately based on the GCTP standard. For example, it may be important to consider whether the evaluation of the process to remove impurities, the examination of the quantity of remaining impurities, the examination of the constitution of cell class before and after the differentiation of cells, and the variety of cell characteristics, are performed appropriately. The specification of the final product must also be considered. For example, the specification depends on cell counts, cell survival rates, tests of purity and sterility, mycoplasmal negation tests, titre examination, and dynamic compliance tests.

The major aim of the GCTP standard is to set an appropriate quality target to continuously monitor and improve the process based on the control and acceptance of risk for each product in terms of manufacturing facilities and quality management systems [10]. It is necessary to establish quality management systems based on the documentation of each step in the production process. The control of sterility is a particular challenge in the production of regenerative medical products. Because regenerative medical products are derived from living cells and tissues, it is difficult to sterilize ingredients before and during the manufacturing process. Contamination can occur during the manufacturing process and the contaminated cells can proliferate. A standard for controlling bio-burden remains to be established. Therefore, it is necessary to consider the risk of contamination and the appropriate standard to
control that risk based on the characteristics of each regenerative medical product, the production facility, and the manufacturing process.

Second, the following points are important considerations in terms of safety in non-clinical investigations of regenerative medical products [13]. The clinical applications of cellular and tissue based products are diverse and it is difficult to describe a standard required evaluation of these products. Therefore, the products should be evaluated on a case-by-case basis, depending on the characteristics of individual products. For example, in investigations of effectiveness and performance, it should be considered whether prospective effects such as the expression of function and the durability of action are evaluable or not. In addition, to ensure safe non-clinical investigations, it is important to consider risks based on the characteristics and the usage of the product.

In terms of the clinical evaluation of regenerative medical products, important points can be highlighted from reviews of products already approved in Japan. In the clinical trial of a cultured skin product (Japan Tissue Engineering Co., Ltd.) [14], two patients with serious burns (Burn Index 30–90%) were included. One displayed 100% epidermization and the other displayed 50% epidermization. There were no serious adverse events. The product was finally approved for limited use in serious burn patients because the benefits for such patients were considered to be superior to the potential unknown risks. This example raises the important point that the conditions of approval can be changed based on the risk/benefit balance for the individual product, the clinical application (especially related to the seriousness of disease and the existence of alternative treatments), and the unexpected risks, in particular, infection.

The efficacy of a cultured cartilage product (Japan Tissue Engineering Co., Ltd.) was investigated in a non-controlled, non-randomized, non-blinded clinical trial. The product was transplanted in 32 cases; 20 cases of traumatic cartilage deficiencies, six cases of osteochondritis dissecans, and six cases of osteoarthritis [15]. In 23 of the 24 evaluable cases, clinical manifestations improved and there were no serious adverse events related to the product. However, meaningful evaluation was difficult because of the non-controlled, non-randomized, non-blinded study design, and different diseases included. Reanalysis was performed only for cases of cartilage deficiencies of more than 4 cm². The product was finally approved under post-marketing surveillance of all cases based on the clinical benefit for intractable injuries. This case demonstrates that even non-controlled, non-randomized, non-blinded trials may contribute to clinical data for marketing approval. However, the clinical position and risk-benefit balance must be considered.

2. Discussion

In the development of regenerative medical products, there are different problems to those faced in the development of conventional pharmaceuticals and medical devices. Use of the products often involves specific techniques for transplantation and collection, and the level of experience of medical institutes and individual practitioners may affect the results of clinical trials. In addition, because regenerative medical products are generally used to treat intractable diseases or injuries it is difficult to perform major randomized clinical trials. Furthermore, the quality of products is more heterogeneous compared with other chemical or biological products because the products involve living cells or tissues and the quality of ingredients can vary according to the donor. The products carry greater risks of infection, tumorigenicity, and immune reactions than conventional pharmaceuticals. Therefore, conventional development procedures and methods of regulatory review may not be suitable for regenerative medical products. The Japanese Government has moved to make Japan an attractive venue for researchers and sponsors based on its strategy for medical innovation. With this aim in mind, the new category of regenerative medical products and the system of conditional/time-limited authorization was established in the PMD Act [1].

The conditional/time-limited authorization for regenerative medical products is a type of adaptive licensing [16], which is defined as a prospectively planned, flexible approach to the regulation of drugs and biologics. In the present situation, the costs of developing pharmaceuticals and medical devices have been increasing, and the development of regenerative medical products may involve additional costs because of the background issues discussed above. Adaptive licensing is intended to decrease the cost of incremental gains in health benefits within an environment of strained budgets. This concept is adopted in marketing approval for regenerative medical products and is also expected to decrease the cost of development.

For conditional/time-limited authorization of regenerative medical products, the initial level of clinical evidence may be suggested in some points referred from the concept of adaptive licensing [17]. From investigators point of view, the surrogate endpoint, which is not fully validated, will expected to be acceptable in some situations and more enriched patients can be included in the trials. These points are sometimes acceptable in present clinical trials for cancer or orphan diseases, but the effectiveness of regenerative medical products is so varied that it is more difficult to determine the true clinical endpoints and appropriate inclusion criteria. The problem of statistics is more serious. Because clinical trials for regenerative medical products often have few cases and the data represents a wide variation in cases and responses, determining the appropriate statistical analysis is particularly challenging. From investigators point of view, it could be appropriate to apply wider significance levels than that used in conventional trials, particularly in the initial review. In some special cases such as intractable diseases or diseases with no alternative treatments, single-arm, observational studies utilizing the registry of the natural course of disease, or exploratory trials, will also expected to become pivotal for initial reviews. Even in these trials, acute adverse events can be identified, and data on rare and difficult-to-detect adverse events have to be collected and reviewed through post-marketing surveillance with the registry.

Some points about the appropriate management of conditional/time-limited authorization under the aforementioned conditions should be considered. First, the valid and feasible management of a post-marketing registry is essential to the approval process. If the registry does not work effectively, not enough data would be gathered until the re-review period, and it would be necessary to perform larger and longer trials in the initial review period. To increase the feasibility of the management of the registry for PMDA, collaboration with major academic societies and hospitals is necessary to collect enough data in the post-marketing period. In addition, continuous support from the national budget and industrial consortiums becomes important to the sustainable management of the registry.

Second, valid registries should be established for the natural course and conventional treatment of the diseases in question to strengthen the feasibility of single-arm studies. There are some small registries for rare diseases in Japan, but they are not fully validated for the review process. Validated data derived from major registries may support conditional/time-limited authorization. Third, the establishment of an objective committee to evaluate effectiveness should be considered in the relevant academic society. Data monitoring committees have the task to monitor the
effectiveness and safety of clinical trials, but the primary evaluation should be performed more objectively if single-arm or observational studies are utilized in the development of regenerative medical products. If the human resource for objective evaluation is limited, it may be appropriate to establish evaluating committees from the academic arena related to the product under investigation.

The changes to the regulatory framework for regenerative medical products may facilitate research and development and contribute to the safety of regenerative medicine in Japan. The framework may also be beneficial to patients because it increases the opportunity for them to receive a new treatment for an incurable disease while providing more information about safety and efficacy of the products. The appropriate management of this new framework will ensure that Japan becomes an attractive venue for the future development of regenerative medical products.

Disclaimer

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