



Original article

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



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ARTICLE INFO

Article history:

Received 16 January 2015

Received in revised form

7 April 2015

Accepted 19 April 2015

Keywords:

Regenerative medical products

Regenerative medicine

Regulation

ABSTRACT

The Japanese regulatory framework for pharmaceuticals and medical devices has recently been reexamined and the revised Pharmaceutical Affairs Law, which has been renamed the Pharmaceuticals, Medical Devices and Other Therapeutic Products Act, was developed in 2013 and implemented in November 2014. In the revised Act, regenerative medical products are newly categorized and independent from conventional pharmaceuticals and medical devices. This enables these products to be reviewed more appropriately and allows for conditional/time-limited marketing authorization. Following the implementation of the new Act, the Good, Gene Cell and Tissue Manufacturing Practice was established to address the different requirements and concepts for appropriate research and development of regenerative medical products. Based on these changes to the regulatory framework for regenerative medical products in Japan, this article aims to examine how this framework could be utilized as an appropriate system to develop innovative regenerative medicine.

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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 November 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. As part of

Abbreviation: PMD Act, Pharmaceuticals, Medical Devices and Other Therapeutic Products Act; RMP Act, Regenerative Medicine Promoting Act; MHLW, Ministry of Health, Labour and Welfare; PMDA, Pharmaceuticals and Medical Devices Agency; GCTP, Good, Gene, Cellular and Tissue-based Products Manufacturing Practice.

[☆] Peer review under responsibility of the Japanese Society for Regenerative Medicine.

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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 endocranium, 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, mycoplasma 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

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