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Original article

A study on ensuring the quality and safety of pharmaceuticals and medical devices derived from the processing of allogeneic human somatic stem cells☆

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ABSTRACT

As a series of endeavors to establish suitable measures for the sound development of regenerative medicine using human stem cell-based products, we studied scientific principles, concepts, and basic technical elements to ensure the quality and safety of therapeutic products derived from allogeneic human somatic stem cells, taking into consideration scientific and technological advances, ethics, regulatory rationale, and international trends in human stem cell-derived products. This led to the development of the Japanese official Notification No. 0907-3, "Guideline on Ensuring the Quality and Safety of Pharmaceuticals and Medical Devices Derived from the Processing of Allogeneic Human Somatic Stem Cells," issued by Pharmaceuticals and Food Safety Bureau, Ministry of Health, Labour and Welfare of Japan, on September 7, 2012. The present paper describes the background information and development of our study and the resulting guidance. For products derived from allogeneic somatic stem cells, major points to consider include 1) history, the source, and derivation of starting cells; 2) donor screening/testing and donor eligibility, especially in relation to the presence of adventitious agents, potential occurrence of donor-derived diseases, and immunocompatibility; 3) clinical records of a donor; 4) multipotency and self-replication ability of allogeneic human somatic stem cells; 5) cell banking; 6) potential presence of viruses in the final product; 7) extensive characterization of the cells at critical stage(s) of manufacture; 8) robustness of the manufacturing process; 9) quality consistency of the products such as the final products and critical intermediate(s) if any; and 10) robust application and function of the final products in a cell environment different from where the original cells were localized and were performing their natural endogenous function. The ultimate goal of this guidance is to provide suitable medical opportunities as soon as possible to the patients with severe diseases that are difficult to treat with conventional modalities.
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☆ Recently, this type of product has been defined as a distinct product from both conventional pharmaceuticals and medical devices according to the revised Pharmaceutical Affairs Law -renamed the Pharmaceuticals and Medical Devices, and Other Therapeutic Products Act. (Akinori Hara, Daisaku Sato, and Yasuyuki Sahara: New Governmental Regulatory System for Stem Cell–Based Therapies in Japan. *Therapeutic Innovation & Regulatory Science*. 2014; **48**(**6**): 681-688.)

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1. Background (chronology and focus of the research)

The details of the present study were described in a previous paper[1)]. The present paper summarizes points that are closely related to those presented in the earlier paper.

Regenerative medicine using cell-based products that are derived from the processing of human cells and tissues is keenly anticipated in Japan because of difficulties with securing human organs and tissues in our country. With technology breakthroughs and research advances, people are increasingly hopeful that medical technology using novel cell-based products will develop into new therapies.

In Japan, translational research to regenerative medicine is advancing rapidly. In particular, considerable work has been done to develop products that make use of human stem cells, i.e., somatic stem cells such as mesenchymal stem cells, embryonic stem (ES) cells, and induced pluripotent stem (iPS) cells. Thus, there is an urgent need to prepare relevant guidelines on the evaluation of products expected in the near future. Identifying at an early stage of development the technical, medical, and ethical conditions necessary for the utilization of various types of stem cells at an early stage of development is vital for their rapid application to the treatment of patients.

In the fiscal year 2008, the Japanese Ministry of Health, Labour and Welfare convened a panel of experts: the "Study Group on Ensuring the Quality and Safety of Pharmaceuticals and Medical Devices Derived from the Processing of Human Stem Cells." The panel was established as a scientific research project of the Japanese Ministry of Health, Labour and Welfare and has been chaired by Dr. Takao Hayakawa since its conception.

The objective of the study group is to promote the sound development of products derived from human stem cells by investigating scientific and technological advances, ethics, the regulatory rationale, and international trends regarding human-stem-cell-derived products and to establish and implement appropriate safety evaluation criteria.

As a result of analyses conducted up to 2009, in accordance with the Pharmaceutical Affairs Law, and with clinical application of the products derived from human somatic stem cells, iPS cells, ES cells, and other relevant cells as the goal, the study group concluded that the appropriate relevant guidelines should be tailored to specific cell sources and phenotypes (human autologous versus human allogeneic; somatic stem cells vs. iPS cells vs. ES cells vs. other cells) to facilitate efficient, effective, and rational research and development (R&D). Points to be considered include but are not limited to technical details, the manufacturing process, characterization, quality control, and stability evaluation, and the data necessary to guarantee the safety and efficacy of the products.

With this perspective in mind and with the desire for consistency in scientific principles and concepts, 2 interim reports on draft guidelines on autologous human somatic stem cell-based products and autologous human iPS cell-based products were prepared in 2009 according to Japanese Ministry of Health, Labour and Welfare Notification No. 0208003. Three other interim reports of draft guidelines on allogeneic human somatic stem cell-based products, allogeneic human iPS cell-based products, and human ES cell-based products were also prepared according to Japanese Ministry of Health, Labour and Welfare Notification No. 0912006. These 5 sets of draft guidelines were thoroughly discussed from a variety of viewpoints. They were then widely circulated among interested parties as articles in a relevant scientific journal to allow readers to comment (Hayakawa T., et al.: Regenerative Medicine [Journal of the Japanese Society for Regenerative Medicine], 9, 116–180 [2010], in Japanese). Thereafter, these articles were updated and published as 8 articles (Journal of the Japanese Society for Regenerative Medicine, 10, 86–152 [2011], in Japanese) that served as the basis for the final draft guidelines. After extensive discussions with the study group and after public consultation, the Pharmaceuticals and Food Safety Bureau of the Japanese Ministry of Health, Labour and Welfare issued 5 notifications on September 7, 2012, as described in the previous paper [1].

In the present paper, a continuation of the previous article, we introduce the basic technological requirements for ensuring the quality and safety of pharmaceuticals and medical devices derived from the processing of allogeneic human somatic stem cells. The final products derived from the processing of allogeneic human somatic stem cells, which are multipotent and retain the ability to self-replicate, should exhibit cell characteristics different from those of the starting cells as a result of cell processing and may be applied and can function at a site (cell environment) different from where the original cells were localized. These concerns have been added to Notification No. 0912006, which serves as the basis for the present guideline.

Before interpreting and implementing the present guideline, the following points should be considered. The ultimate goal is to provide patients with new therapies that utilize regenerative medicine. The role of the guideline is to present the scientific principles, concepts, ideas, and technical elements that will help to achieve the specified goal in the most efficient and effective manner possible. Because situations, circumstances, and products will vary, the guideline addresses the points of concern in a comprehensive manner. Therefore, it is important to identify the relevant testing parameters and evaluation methods by taking into consideration the characteristics of the cells in question, the specific clinical objective, and the method of application. Those that are applicable should be justified and implemented in an appropriate and flexible manner.

Several points should be kept in mind with respect to the development of medicinal products for regenerative medicine and throughout the implementation of this guideline. The desired products are expected to show a potential as a novel therapeutic method as a result of relevant proof of concept (POC). Relevant data and/or information should establish that there are no critical concerns for product safety that might impede the use of the products in humans for the first time. Thorough observance of the Declaration of Helsinki, including proper informed consent and right of self-determination on the part of the patient, is indispensable.

It should be emphasized again that the primary goal of our endeavor is to offer suitable treatment options as soon as possible to patients with severe diseases that are difficult to treat with conventional modalities. The present guideline should be useful for this purpose. Therefore, it is important to interpret and employ the guideline in a flexible and meaningful way. Stringent observance of the guideline without taking into account the patients and their specific situation (which is like putting the cart before the horse) should be avoided.

It is evident that progress in the application of regenerative medicine is desirable for maintaining and improving human health. The development of innovative and revolutionary medicinal products and therapeutic techniques should benefit our country as well as the international community. Regenerative medicine is a great way to make a peaceful international contribution that will be a legacy for mankind. In this context, the role of the government is to promote clinical research and industrialization; regulations and guidelines are adopted so that we advance towards this common goal in a scientific, rational, efficient, and effective manner. All those involved, like players with a common goal in the same arena, should continue to make efforts to deliver to patients as soon as possible the revolutionary cell-based products and therapeutic techniques.

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