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Original article

A study on ensuring the quality and safety of pharmaceuticals and medical devices derived from the processing of human embryonic 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 the processing of human embryonic stem cells (hESCs), 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. 0907-6, "Guideline on Ensuring the Quality and Safety of Pharmaceuticals and Medical Devices Derived from the Processing of Human Embryonic Stem Cells," issued by Pharmaceuticals and Food Safety Bureau, Ministry of Health, Labour and Welfare of Japan, on September 7, 2012. The present paper addresses various aspects of products derived from hESCs, in addition to similar points to consider that are described previously for allogeneic human stem cell-based products. Major additional points include 1) establishment of hESCs; 2) establishment of stable and well-characterized cell banks of hESCs and relevant intermediate cell products; 3) concerns about the presence of undifferentiated cells in final products, which may result in ectopic tissue formation and/or tumorigenesis; and 4) concerns about undesirable immunological reactions caused by the final products. The ultimate goal of this series of guidelines on regenerative medicine is to provide suitable medical opportunities as soon as possible to the patients with severe diseases that are difficult to treat with conventional modalities. If these guidelines are interpreted and employed in a flexible and meaningful way in this context, they should serve as a useful means to achieve their goals.

☆ 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 the previous papers [1–4]. The present article 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 on 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 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 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, the study group concluded that 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 R&D. Points to be considered include but are not limited to relevant technical details, the manufacturing process, characterization, quality control, 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 Pharmaceutical and Food Safety Bureau of the Ministry of Health, Labour and Welfare of Japan issued 5 notifications on September 7, 2012, as described in the previous paper [1].

In the present paper, a continuation of the previous articles [1–4], we introduce the basic technological requirements for ensuring the quality and safety of pharmaceuticals and medical devices derived from human ES cells.

Human ES cells can provide raw material for the production of a variety of cell types because of their pluripotency, which is greater than that of somatic stem cells, whose ability to differentiate and self-replicate is limited. Once effective and efficient differentiation protocols for the generation of a target cell lineage are established, human ES cells are expected to stably supply large amounts of cell substrates for use in cell-based therapies.

Human ES cell-based products were recently evaluated in clinical trials in the USA. However, human ES cells are generated by destruction of human embryos. Because this approach raises ethical issues, the generation and use of human ES cells require careful consideration. To ensure human dignity, the derivation, distribution, and utilization of human ES cells should adhere to the "Guidelines for the Derivation and Distribution of Human Embryonic Stem Cells" (Japanese Ministry of Education, Culture, Sports and Technology Notifications No. 156 of August 21, 2009, and No. 86 of May 20, 2010) and the "Guidelines for the Utilization of Human Embryonic Stem Cells" (Japanese Ministry of Education, Culture, Sports and Technology Notifications No. 157 of August 21, 2009, and No. 87 of May 20, 2010). In these 2 guidelines, basic issues concerning the protection of personal information and protocols for the derivation and use of human ES cells are defined from the standpoint of bioethics. According to the guidelines, the derivation and use of human ES cells from human fertilized embryos is permitted only for basic research that serves to elucidate human development/differentiation and tissue regeneration or to develop new diagnostic methods, approaches to prevention or treatment, or products intended for medical use.

The goal of basic research that contributes to the development of "new diagnostic methods, approaches to prevention or treatment, or products intended for medical use" can be interpreted to mean the development of novel treatments, pharmaceuticals, and medical devices.

We developed a draft guideline containing the points to consider for ensuring the quality and safety of cellular products throughout the process, beginning with the establishment of human ES cells. The draft guideline by this research team can be practically applied at present to pharmaceuticals and medical devices manufactured by producing differentiated cells from preexisting ES cells. However, in the future, another guideline also needs to be prepared for pharmaceuticals and medical devices derived from the processing of newly established human ES cells.

When human ES cells are used a source of cell substrates for the manufacture of cell- and tissue-based products, data and information on their characteristics and competence as raw materials should be comparable to those described in the "Guidelines on Ensuring the Quality and Safety of Pharmaceuticals and Medical Devices Derived from the Processing of Allogeneic Human Cells" (Notification No. 0912006; from the Director of the Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare of Japan) in order to ensure the quality and safety of the final products. This is because the clinical application of products made from both cell types is allogeneic in nature. Thus, the extent and depth of evaluation, particularly in terms of adventitious agents and immunogenicity, should be equal for both cell types.

At present, however, the notifications of the Japanese Ministry of Education, Culture, Sports, Science and Technology (No. 156 and