Development of Novel Advanced Cell and Gene Therapy and GMP-Controlled Cell Processing

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Abstract: High scientific and ethical practices and reliability in compliance with the ICH-GCP (International conference on harmonization-good clinical practices) are properly required for clinical trials/research involving human subjects. Cell therapy is a general term for treatment modalities conducted by transplantation of human cells, such as blood transfusion, hemopoietic stem cell transplantation, cell transfer immunotherapy, gene therapy, and regenerative therapy. A production system called cell processing including human cell preparation, cultivation, and gene transduction is essential for the development of therapies using cells, and the quality control thereof must be performed in compliance with the good manufacturing practice (GMP). At the moment, however, Japan is far behind in the formulation of rules for cell processing, which should be evolved without delay in order to promote the development of advanced therapy. In particular, it is urgent to construct an institutional GMP (iGMP) specialized for academic institutions and centers, where development of advanced therapy such as regenerative therapy and cell therapy is being undertaken.

Key words: Development of novel advanced therapy; Cell therapy; Regenerative therapy; Gene therapy; Cell processing

Introduction

In view of the life science research evolving with remarkable progresses since the beginning of the 21st century, it is eagerly awaited that the results of basic research would be fruitfully translated into effective therapeutics for patients with incurable diseases. The term “cell therapy” includes much of regenerative therapy, immunotherapy and gene therapy that progress based on novel theories or strategies. High scientific and ethical practices and reliability are required for the development of such edge-cutting advanced therapies.
Currently, drugs used in clinical settings are manufactured in compliance with the current good manufacturing practice (GMP), the standards for production and quality control of drugs. In Europe and the United States, GMP-controlled cell processing is mandatory for the development of translational research using human cells per se to treatment.

Rationale of the Need for GMP-Compliant Cell Processing

Development of a new drug, based on basic research data, proceeds to preclinical studies and further to phase I trials. The drug used in these studies should be produced under GMP control. In the States, an investigational new drug (IND) authorized by the Food and Drug Administration (FDA) is used in clinical trials, and a similar system is being implemented for drugs in Japan as well. Deduced from these principles, it is readily understandable that production of human cells for clinical use must also be in compliance with the GMP when those cells are considered to represent “cell pharmaceuticals”.

The prototype of cell therapy is blood transfusion, and blood products are prepared in accordance with the GMP at blood centers or blood banks. It is essential that individual products be checked for potentially transmissible infectious agents since human cells, which unlike drugs do not constitute batches, are used. Most translational researches with the use of human cells are conducted at academic institutions and centers for novel advanced therapy. No one would allow the transplantation of cells prepared at a conventional laboratory without any defined standards or records.

The System in the United States and Current Status in Japan

In January 2001, the US FDA proposed the current good tissue practice (cGTP), which specifies those matters required for the production of human cells for therapeutic use, particularly to prevent transmission of infections, and finalized in November, 2004. Further, the sterile drug products produced by aseptic processing was also finalized by the Center for Drug Evaluation and Research (CDER) in September 2004.

It states, “Poor cGMP conditions at a manufacturing facility can ultimately pose a life-threatening health risk to a patient” in the introduction section, and provides concrete descriptions of an aseptic processing facility design layout, aseptic processing techniques and management. The CBER focuses primarily on the aseptic processing for drugs, but also gives consideration to applicability of the standards to cell processing.

In Japan, it is stipulated in the Amended Pharmaceutical Affairs Law enforced as of July 30, 2003, that “regarding ‘Biological Products’ which require advanced production process control, the premises and the procedures of production and quality control at the manufacturing facility (annotation by the author: the so-called GMP) shall comply with the manufacturing standards for ordinary drugs and medical devices and, in addition, shall comply with the supplementary standards laid down by the Ministry of Health, Labour and Welfare”. A subordinative law will be issued in April, 2005.

FDA’s Guiding Principles for Development of Advanced Cell Therapy

When intending to carry out development of cell therapy in the States, researchers or clinical investigators should prepare a clinical trial protocol and submit documents required for GMP-controlled cell processing to the FDA. The FDA evaluates the cells for therapy as an IND to be used in translational research, inspects the manufacturing facility, and guides the applicant in preparing GMP-related documents.

The FDA officer recognizes the disparity between the GMP for conventional drugs and
that required for cell processing, and is ready to lend his/her cooperation in establishing an institutional GMP necessary for translational research, with actual situations in academia taken into account, based on full GMP required for pharmaceutical manufacturers to follow in the production of commercial products (Fig. 1). Thus, in the States, a national strategic stance is being taken to actively aid academic institutions in the development of a novel therapy, concerning that the motivation for developmental research will be diminished because of the lack of clearly established standards.

Points at Issue in Japan

There is an opinion that “construction of GMP-controlled cell processing may well be left to the hands of enterprises or companies”. It is anticipated, indeed, that manufacturers can make inroads into the area such as cultured skin, where products are already in clinical application. However, what are developed in academia or centers for advanced therapy are for the most part those products manufactured through translational research based on results of basic research, and are yet to be determined as to whether they can be established as novel therapeutics.

It is difficult for a pharmaceutical company to make a positive entry into the development of GMP-controlled cell processing without running a risk at such a stage of translational research. Therefore, researchers, clinical investigators, pharmacists, medical technologists (biologists), engineers, GMP consultants, and researchers of corporate advanced medicinal development divisions should closely collaborate in constructing the standards based on global rules specialized for academia and centers for advanced therapy.3)

Summary and Conclusion

It has become recognized at length in Japan that the cell processing control bodies must be ready for the development of cell therapy and regenerative therapy. However, some institutions are still carrying out parallel incubation of cells from several different individuals within the same incubator with a clean bench settled in a conventional laboratory, or are performing...
co-cultivation with murine cells or administration of cells grown in cultures with fetal bovine serum simply because such has been approved by a local ethical committee. No one would allow, even though indirectly, a transplantation of or being injected with an article which one even hesitates to eat.

There is no law to regulate such a situation at present in Japan. GMP-controlled cell processing is thus definitely needed all the more for culturing human cells and performing gene transfection in the advanced medical treatment where safety and efficacy have not been fully verified, especially in cell therapy and regenerative therapy. This constitutes basic rules that all individuals engaged in the development of advanced medical treatment must observe. Stringent regulation is required all the more in such experimental exploratory treatment of which safety and therapeutic effects are yet to be established. Research and development starting in a slovenly manner will yield irreparable results. It should be done in strict accordance with regulations until “the cell processing is thought to be infallibly safe up to the proven level”, so that due deregulation then may gradually follow.

Establishment of institutional GMP for academia and centers for advanced therapy is mandatory for the development of advanced therapy in terms of cell therapy, and a keen insight from those concerned are greatly expected.

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REFERENCES

