Biologicals 43 (2015) 410–415

Contents lists available at ScienceDirect

Biologicals

journal homepage: www.elsevier.com/locate/biologicals

Meeting report

Overview: Core technical elements for early product development, evaluation, and control of human cell-based products

Takao Hayakawa [a, b, c, *]

[a] Pharmaceutical Research and Technology Institute, Kindai University, Japan
[b] National Institute of Health Sciences, Japan
[c] Graduated School of Medicine, Osaka University, Japan

ARTICLE INFO

Article history:
Available online 10 August 2015

Keywords:
Cell therapy
Cell-based products
Essential scientific elements
Product evaluation and control
Early product development
Product quality and safety

ABSTRACT

Essential scientific elements for early product development, evaluation, and control of human cell-based products for cell therapy are addressed in a comprehensive and unifying way. Among them, donor issues (autologous and allogeneic), testing of raw materials, cell banking and cell substrate characterization, testing for adventitious agents (viral safety), and product sterility are very much related to each other. A significant amount of expertise exists in these areas both for traditional biologicals as well as for biotechnology products. Thus, core principles/concepts as well as the testing methodologies are already well defined. Other critical technical elements that are essential but need further discussion in terms of relevant regulatory requirements and testing methods are touched upon very briefly and followed by a detailed discussion (elsewhere).

1. Introduction

Cellular therapies using relevant products derived from the processing of human cells are keenly anticipated around the world because of the limited supply of human organs and tissues for transplantation and a lack of a cure for various severe diseases. With technology breakthroughs and research advances, people are increasingly hopeful that medical technology involving novel cell-based products will develop into actual treatments.

To make sure that novel human cell-based products contribute more to human health care, it is essential that, based on sound scientific rationale and approaches at that point in time, suitable measures be taken by the manufacturers and regulatory authorities regarding application of these products to patient care by taking into account specificity of the manufacturing process, products, administration procedures, and diseases in question.

There is a long history of regulation of traditional biological/biotechnological products, and guidance documents exist at international levels, including Harmonised Tripartite Guideline that are developed by International Conference on Harmonization (ICH) and WHO written standards, the scientific concepts/principles of which may be particularly relevant to those of cell therapy products [1–7]. For cell therapy products a variety of guidelines and regulations currently exist or are in development by both governmental and professional organizations in different regions of the world where cell therapy research and development activities are underway [8–14]. As a result, there is a need for a global effort to develop a set of common principles that may serve to facilitate a convergence of regulatory approaches to ensure the smooth and efficient evaluation of novel cell-based products expected in the near future.

Among the various core elements of a cell therapy involving human cell-based products, this paper is focused on core technical elements for early product development, evaluation, and control of human cell-based products.

2. General considerations on sound scientific requirements for product development, evaluation, and control

There are many types of manufacturing methods, types, and characteristics of the desired cell products, and types of clinical applications. In addition, scientific progress in this field is incessant, and expertise and knowledge are constantly accumulating. Therefore, it is not always appropriate to consider the present paper all-inclusive and definitive. Consequently, when testing and evaluating each product, it is necessary to consider it on a case-by-case basis using a flexible approach based on rationale that reflects the scientific and technological advances at that point in time.

The main purpose of evaluating quality and safety of the desired cell products before conducting investigational clinical trials is to

* Pharmaceutical Research and Technology Institute, Kindai University, Japan.
E-mail addresses: takao-hayakawa@mtg.biglobe.ne.jp, hayakawatakao@gmail.com.

http://dx.doi.org/10.1016/j.biologicals.2015.05.010
1045-1056

determine 1) whether there are any quality and/or safety problems that would obviously hinder initiation of human clinical trials of the products in question, 2) whether certain quality attributes (QA) of the product are understood sufficiently to establish a relationship between the clinical findings and the QA, and 3) whether consistency of the QA can be ensured within a definite range.

Simultaneously, it is important to eliminate as much as possible any known risk factors associated with product quality and safety using up-to-date science and technology and to describe the scientific validity of the results of such action. The remaining presumed risk factors should be weighed against the risks associated with not performing the trials in patients who suffer from diseases that are serious and life-threatening, that involve marked functional impairment, that lead to a marked decrease in quality of life (QOL) resulting from the loss of a certain degree of a physical function or form, or for which existing therapies have limitations and do not result in a cure. Furthermore, it is important to entrust the patient with the right to make a decision after receiving all of the available information. When applying for approval of investigational clinical trials, applicants can submit a provisional nonclinical data package, which is prepared reasonably by taking into account product aspects and patient aspects including a balance between the risk of the product versus the risk that a patient faces with/without treatment in question, in order to decide to initiate investigational clinical trials, on the premise that the data package submitted at the time of the marketing application/registration to ensure quality and safety will be enriched and developed as the clinical trial progresses.

Applicants are encouraged to discuss with the relevant regulatory agency the type and amount of data that may be needed to initiate an individual clinical trial. Because of differences in product origin, target disease, target patients, application sites, application methods, and processing methods, there may be numerous variations among individual data packages; these differences cannot be definitively clarified in the present document.

The items, test methods, criteria, and any other technical requirements described in the present paper are intended to be considered, selected, applied, and evaluated to serve each intended purpose; they do not necessarily require the most stringent level of interpretation and practice. In accordance with the purpose of the present paper, applicants are encouraged to explain why the background, selection, application, and the content and extent of evaluation are appropriate and scientifically rational.

3. Basic scientific issues for early product development, evaluation, and control

Basic scientific issues for early product development, evaluation, and control include:

1) Justification of the source and selection of human cells that serve as raw materials, including autologous or allogeneic donor screening criteria and eligibility
2) Suitability and quality control of raw materials and manufacture-related substances other than the target cells
3) The expected function and safety of noncellular components (NCCs) constituting the final products together with the cells
4) Establishment of a relevant cell line, cell bank, and/or critical intermediate(s); processing of the cells
5) Preparation of the desired cell products
6) Formulation (preparation of the final product)
7) Characterization and understanding of specific profiles of cells at critical stages (e.g., starting, bank, intermediate, and final stage)
8) Verification of a manufacturing process and constancy of the manufacture as well as process control
9) Comparability assessment after changes in a manufacturing process
10) Product stability
11) Quality control of final products on the basis of product aspects (including setting of specifications) and process aspects
12) Setting storage and a transport procedure for the cells/products at critical steps

3.1. Justification of the source and selection of human cells that serve as raw materials

For the manufacture of human cell-based products, first, it is necessary to select the source and origin of the cells used as raw materials, and to explain the reasons for selecting these cells. They would be either 1) autologous or allogeneic somatic cells, 2) autologous or allogeneic somatic stem cells, 3) autologous or allogeneic induced pluripotent stem (iPS) cells or iPS-like cells, 4) embryonic stem (ES) cells, or 5) any other human cells.

3.1.1. Donor selection criteria and eligibility

For donor selection criteria and eligibility, it is crucial to indicate that the donor was selected in an appropriate and ethical manner and that the proper procedure was followed. In addition, it is necessary to establish selection criteria and eligibility criteria that take into consideration age, sex, ethnic characteristics, genetic characteristics, a clinical history, the health condition, test parameters related to any type of infection that may be transmitted via cell and/or tissue samples, and immunological compatibility, and to explain their appropriateness. If the donor genomic or gene analysis is undertaken, it shall be performed in accordance with the relevant official guidelines issued by a relevant regulatory authority.

3.1.2. Autologous cells and tissues

As for autologous cells and tissues, it is especially important to provide/consider data on 1) infectious status of the donor, 2) risk of proliferation or reactivation of the virus during the manufacturing processes, 3) robust process control to minimize unevenness of "custom-made" products, and 4) a limited amount of samples for quality evaluation of products.

3.1.3. Allogeneic cells and tissues

As for allogeneic cells and tissues, it is especially important to provide/consider data on the history, source, and derivation; 2) donor screening/testing and donor eligibility (compatibility with donor qualification criteria, including ethical and medical aspects); 3) medical records of the donor; 4) cell banking, 5) potential presence of viruses in products, and 6) immunological problems.

4. Suitability and quality control of raw materials and manufacture-related substances other than target cells

Raw materials and manufacture-related substances other than the target cells may include culture media (all components: e.g., serum, growth factors, antibiotics, and media products such as DMEM and RPMI), feeder cells, materials used for processing of cells (e.g., all chemical reagents, proteins, genes, and vectors as described later), and materials used for formulation. For their suitability and quality control, it is necessary to 1) indicate their appropriateness for the intended use, and if necessary, establish their specifications; 2) perform proper quality control for these