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To: Directors of Prefectural Health Departments (Bureaus)

Director of Medical Device Evaluation Division,
Pharmaceutical Safety Bureau,
Ministry of Health, Labour and Welfare
(Official seal omitted)

Guideline for Comparability of Human Cell-Processed Products Subject to Changes in Their Manufacturing Process

Research on Regulatory Science of Pharmaceuticals and Medical Devices of the Japan Agency for Medical Research and Development (AMED) conducts public research specializing in regulatory science research with the aim of formulating review guidelines and standards based on scientific rationality and social justification, developing evaluation methods for pharmaceuticals and medical devices utilizing cutting-edge technology, and developing international standards and standards ahead of the rest of the world.

As attached, the "Guideline for comparability of human cell-processed products subject to changes in their manufacturing process" and Questions and Answers (Q&A) have been compiled by the Research Group "Study on Equivalence Evaluation Associated with Changes in the Manufacturing Process of Cell Processed Products" (Representative: Yoji Sato, Director, Devision of Cell-Based Therapeutic Products, National Institute of Health Sciences at the time of the start of the Research Group). Please inform manufacturers and sellers placed under your administration to utilize for their business operations.

*This English translation of the Japanese Notification is intended to be a reference material to provide convenience for users. In the event of inconsistency between the Japanese original and this English translation, the former shall prevail.

Attachment

Guideline for Comparability of Human Cell-Processed Products Subject to Changes in Their Manufacturing Process

1.0 INTRODUCTION

1.1 Objectives of the Guideline

The objective of this document is to present the basic concepts for assessing the comparability of human cell-processed products before and after a change is made to the manufacturing process for the target cells or the final product. This guideline is intended to provide advice on what data and information should be collected to establish that changes in the manufacturing process will not have unwanted effects on the quality and efficacy/safety of the final product. The document does not directly prescribe any particular analytical, nonclinical, or clinical strategy. The main emphasis of the document is on quality aspects. Human cell-processed products vary widely in type, characteristics, and clinical applications, and scientific advances and experience in this field are constantly evolving. It may not always be appropriate to apply this guideline uniformly or to deem this guideline to encompass all necessary matters. Therefore, in conducting and evaluating studies on individual human cell-processed products, it is necessary to take a flexible case-by-case approach based on rational evidence that reflects the academic progress at that time, taking into account the purpose of this guideline.

1.2 Background

Manufacturers [1] of human cell-processed products frequently make changes to manufacturing processes [2] of products [3] both during development and after approval. Reasons for such changes include improving the manufacturing process, increasing scale, improving product stability, and complying with changes in regulatory requirements. When changes are made to the manufacturing process, it is common for the manufacturer to first evaluate the relevant quality attributes of the product to demonstrate that modifications did not occur that would have unwanted effects [4] on the efficacy and safety of the product. Such evaluations often indicate whether or not confirmatory nonclinical or clinical studies are necessary.

The existing ICH guidelines and relevant domestic laws and regulations have not specifically addressed considerations for demonstrating comparability of human cell-processed products before and after a change to the manufacturing process. However, several ICH guidelines and relevant domestic laws and regulations have provided referential technical information that can also be useful for assessing process changes for human cell-processed product. (Representative examples are shown in the "References" section of this document.) This document is intended to provide the guidelines necessary to take an approach in terms of quality characterization to demonstrate the comparability of human cell-processed products before and after a change to the manufacturing process, mainly based on the ICH Q5E guideline "Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process."

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[1] In this document, when the term "manufacturer(s)" is used, it is intended to include any party having a contractual arrangement to produce the intermediate products or final product on behalf of the marketing authorization holder (or the developer, if prior to market authorization).

[2] In this document, when the term "manufacturing process(es)" is used, it also includes facilities and equipment that might impact on critical processing parameters and, thereby, on product quality.

[3] In this document, when the term "product(s)" is used, it is intended to refer to the intermediate products and final product.

[4] Improvement of product quality is always desirable and encouraged. Even if there seems to be a difference in evaluation, the difference may be acceptable and appropriate in terms of comparability if the quality has been improved and is considered to have no problems from efficacy and safety viewpoints. In this regard, the manufacturer is advised to consult with the relevant regulatory authority.

1.3 Scope

1.3.1 Applicable Products

The information adopted and explained in this document shall apply to the following:[5]

(A) Human cell-processed products listed in the Appended Table 2 (Related to Article 1-2) of the "Cabinet Order on the Development of Related Cabinet Orders and Transitional Measures Accompanying the Enforcement of the Act for Partial Amendment of the Pharmaceutical Affairs Act, etc." (Cabinet Order No. 269 of 2014);

(B) Products for which changes have been made to the manufacturing process by a single manufacturer (including a single developer seeking marketing authorization) who can directly compare analysis data of the pre- and post-change products; and

(C) Products for which changes have been made to the manufacturing process during development or after obtaining marketing authorization.

1.3.2 Characteristics of Applicable Products

Applicable human cell-processed products shall refer to regenerative medical products specified in the "Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices" that are manufactured by culturing or otherwise processing human cells. Because human cell-processed products contain complex and heterogeneous viable cell components, it should be noted that their critical quality attributes (see Section "3.0 Glossary") cannot always be observed comprehensively, and that they cannot always be characterized using an existing set of analytical procedures like biopharmaceuticals (biotechnological/biological products), which are produced from recombinant or non-recombinant somatic cell protein expression systems by culture and highly purified. On the other hand, it is also possible that, in the evaluation of the comparability of human cell-processed products, the decision may be made not only on the basis of characterization, but also on other factors (e.g., rationale differences[6] in the manufacturing process to be changed). As for the sufficiency of the comparability assessment following changes in the manufacturing process of individual products, the manufacturer is advised to consult with the relevant regulatory authority.

The information presented in this document may also be useful as a reference for comparability assessments of products outside the above categories, such as regenerative medical products other than human cell-processed products, and products containing extracellular vesicles like exosomes as the main components. However, as to how the information presented in this document should be used as reference, the manufacturer is advised to consult with the relevant regulatory authority.

[5] This document applies to situations in which all of the three conditions are present. It is required to assess the comparability of a product under development as a subject of public regulation, if data obtained through quality and nonclinical studies of the product before a change is made to the manufacturing process are to be used as analytical data for the product after the process change is made. Product quality characteristic data that are not related to the efficacy and safety of the product for clinical use may be compared to solve problems in development among the developers, but are outside the scope of comparability assessment in this document.

[6] For example, it may be reasonable to explain that "there is no rationale difference because the automated culture process mimics the operator's manual work" when changing from a manual culture process to a machine-automated culture process, or to explain that "there is no rationale difference because the shear stress on the cells is matched in calculation although the rotation speed is changed" when changing the culture scale in a rotating suspension culture system.

1.4 General Principles and Basic Concepts for Human Cell-Processed Products

1.4.1 General Principles

The goal of the comparability exercise is to ensure the quality, efficacy, and safety of the final product manufactured by a changed manufacturing process. To meet this goal, it is necessary to collect and evaluate appropriate data and examine whether the process change may have any unwanted effects on the final product.

Demonstration of "comparability" does not necessarily mean that the quality attributes of the pre- and post-change products are completely identical, but that they are highly similar and that the existing knowledge is sufficiently predictive to ensure that any differences in quality attributes have no unwanted effects on the efficacy and safety of the final product.

Comparability is assessed in light of the efficacy and safety of the final product based on a combination of characterization of cells and human cell-processed products by physicochemical testing or biological assays, manufacturing process factors and, in some cases, nonclinical and clinical data. If comparability before and after the process change can be assured through physicochemical and biological test results alone, nonclinical or clinical study data using the product after the change will not be necessary. However, if the relationship between quality attributes and efficacy/safety has not been fully elucidated, and if any changes are observed in the quality attributes of the products before and after the process change, it would be appropriate to perform a comparability exercise in combination with nonclinical and clinical studies (including phase 4 clinical studies [post-marketing clinical studies] on efficacy and safety) in addition to quality-related studies.

To identify the possible effects of a process change, it is necessary to carefully evaluate all foreseeable consequences for the product. Based on this evaluation, criteria should be established to determine that the pre- and post-change products are highly similar, i.e., that the existing knowledge is sufficiently predictive to ensure that any differences in quality attributes have no unwanted effects on the efficacy and safety of the final product. Generally, the first step is to accumulate data on the quality of the product before and after the process change. Then, the quality data should be compared by comprehensively evaluating all quality evaluation data obtained; for example, routine batch analyses, in-process control, manufacturing process verification/process validation/process evaluation data, characterization and, if appropriate, stability data. Comparability between the pre- and post-change products shall be evaluated objectively by comparing the obtained results against the predefined criteria. In doing so, it is useful to establish the priority of quality attributes to be evaluated as a basis for assessing the comparability according to the clarity of the relationship with efficacy or safety, and the significance of the impact. Critical quality attributes are indispensable for evaluation. It is assumed that this evaluation of quality should always be linked to the efficacy and safety of the final product.

Evaluation of quality attributes will allow the manufacturer to respond with one of the following outcomes:

(A) On the basis of the comparison of relevant quality attributes to the extent technically possible and scientifically reasonable in light of the current state of science and technology, the pre- and post-change products are highly similar and the change does not affect quality attributes that are essential for ensuring the efficacy and safety of the product (critical quality attributes), i.e., the products are considered to be comparable and are not likely to have an adverse effect on efficacy and safety;

(B) Although the pre- and post-change products appear to be highly similar, there are some differences in their quality attributes before and after the process change. However, the pre- and post-change products may be considered to be comparable based on experience and relevant information and data accumulated so far if it is

considered that there is no unwanted effect on efficacy or safety.

(C) If the pre- and post-change products appear to be highly similar, but changes that could affect the efficacy and safety of the product cannot be adequately identified by the analytical method used, consideration should be given to conducting additional quality studies (e.g., characterization) or nonclinical or clinical studies in order to draw definitive conclusions.

(D) Although the pre- and post-change products appear to be similar, differences are identified through comparison of the quality attributes of the products, and it cannot be ruled out that there may be unwanted effects on efficacy and safety. In such cases, it is considered inadequate to determine that the pre- and post-change products are comparable simply by collecting and analyzing additional data on the quality attributes. Therefore, consideration should be given to conducting nonclinical and clinical studies to a certain extent[7] for the assessment of comparability.

(E) If it is strongly suspected that differences in the quality attributes between the pre- and post-change products could adversely affect efficacy and safety, the products cannot be considered highly similar and are not comparable.

1.4.2 Basic Concepts for Comparability Exercise of Human Cell-Processed Products

Unlike low-molecular-weight products and biotechnological products subject to ICH Q5E guideline, for human cell-processed products, there are significant difficulties in comprehensively analyzing and presenting the quality attributes of cells as the active ingredient at a molecular level, whereas it is important to examine the heterogeneity of cell population, phenotypical changes attributable to the surrounding environment (e.g., differentiation and dedifferentiation), and cellular responses to the surrounding environment (e.g., release of bioactive substances).

Therefore, even if all quality attributes measurable with current technology are listed for human cell-processed products, it may not always be assured that all critical quality attributes necessary to fully assure the comparability of efficacy and safety have been completely covered and identified. That is, efforts should be made for the "comparability" of human cell-processed products to approach the target product quality profile as closely as possible with such a limited matrix (combination) of quality attribute indicators, and the comparability is limited to a scope that can be discussed on the basis of between-batch reproducibility assessments. For example, when a manufacturing site is changed or scaled up for the culture of some identical cells, it is possible to define some technically measurable characteristics of the cells to be comparable in terms of their characteristics. Similarly, it may also be possible to discuss the comparability between the pre- and post-change products, with a presupposition of identical cell lines or cell banks, for example, based on the characteristics of various cells before and after changes are made to the processing conditions, including culture, and manufacturing-related materials (ancillary materials), or their matrices, after clarifying their limitations. In cases such as the two examples described above, evaluation should be made with reference to the nonclinical and clinical data that have been obtained as relevant findings so far. If the accumulation of knowledge is insufficient, consideration should be given to performing evaluations, including nonclinical and clinical studies to a certain extent[7] using the post-change product (in this case, minimally required studies should be determined by risk assessment for each product). In any case, it is possible to devise a reasonable evaluation method and to refer to nonclinical and clinical data that have been obtained as relevant knowledge so far, but it is still necessary to have sufficient data for evaluation that allows us to discuss the comparability between

[7] The scope of "a certain extent" varies from product to product. If the results of risk assessment from the quality perspective of the target product reveal potential hazards that can be assumed but for which the relationship to serious risks in humans is unclear, or if hazards that can be clearly associated with serious risks in humans cannot be fully assessed or controlled, consideration should be given to conduct nonclinical or clinical studies using the product after the process change that will at least contribute to the assessment of the risks attributable to these hazards.

the pre- and post-change products. Usually, on the assumption that the post-change final product is to be made available for clinical use, a series of evaluations, including nonclinical studies to an appropriate and reasonable extent, will be required using the product.

When changing cell lines or cell banks as starting materials for manufacturing, it should be noted that it is only possible to discuss whether the cell lines or cell banks are comparable when we can explain the efficacy or safety of human cell-processed products as final products or the comparability in quality attributes that ensure their efficacy or safety, and not vice versa. In other words, it is not always possible to discuss comparability in terms of the quality of human cell-processed products as final products or comparability in terms of the results of nonclinical and clinical studies based solely on the results showing the comparability of cell lines or cell banks in terms of cell characteristics and safety indicators, which are commonly discussed in the field of cell biology. Material cell lines and cell banks are often heterogeneous cell populations; therefore, it is impossible, due to limitations of analytical methods, to reflect and express all characteristics such as distribution and abundance ratio of cell subpopulations (clusters), as well as their response to processing, using only the characteristic indicators commonly discussed in the field of cell biology, and these indicators may not always be sufficient or adequate to cover all the critical quality attributes to be associated for ensuring the efficacy and safety of human cell-processed products. For example, it is known that the percentage of positive cells of various CD antigens, which are widely used as markers of mesenchymal stem cells, do not reflect differences among donors or by passages in the differentiation potential into adipocytes, and cannot be a quality attribute indicator for the differentiation potential of mesenchymal stem cells into adipocytes. It is also known that human pluripotent stem cell lines differ greatly in their ease of differentiation into various types of differentiated cells (directionality) among the cell lines, even when pluripotency marker genes are expressed in the same way. Therefore, it is advisable to have selected starting material cells at least prior to the start of a clinical trial, after thorough consideration during the product development phase. This is because it is not easy to change the starting material cells after approval or to evaluate the validity of new material cells in relation to their quality attributes and clinical efficacy and safety, and it is highly likely that a new clinical study will have to be conducted. In the cell lines and cell banks used as material cells, identification of quality attributes assumed to be related to the efficacy and safety of the final product will contribute to ensuring the quality of raw materials and products and guaranteeing their reproducibility, and will also be a fundamental element in the comparability assessment. In order to enhance the quality attribute profile that is linked to the constant reproducibility of product quality and efficacy/safety, it is advisable to make an effort to explore as much as possible the quality attributes deemed essential and to develop appropriate measurement methods for these attributes while envisioning the final product at the stage of material cells. In making changes at the stage of starting material cells, it is important to conduct more thorough comparative studies of the characteristics of pre- and post-change material cells to obtain useful information as a measure and element that contributes to the comparability assessment of the target final product.

The essence of medical products such as pharmaceuticals, medical devices, and regenerative medical products (including human cell-processed products) is that they have efficacy and safety in their intended clinical use, and the elements that materially guarantee this essence are the quality attributes of raw materials, intermediate products, and final products, and the constant reproducibility of product manufacturing. The quality attributes and manufacturing methods of individual products should be determined independently by their developers. A quality attribute is not always limited to an attribute of a cell; for example, analyzed levels of components in cell supernatants during the manufacturing process or structural forms (e.g., “sheet-like structure” for cultured epidermis products for treatment of burns) may also be important as efficacy- and safety-related quality attributes.

Information obtained from quality attributes of raw materials, manufacturing-related materials (ancillary materials), or intermediate products, and manufacturing processes may be elements that assure the quality of the final product as quality attributes related to the efficacy and safety of the final product. Therefore, in a marketing application, each element of the manufacturing process,

from upstream (starting material) to downstream (final product), should be evaluated on the assumption that it may "complexly define" the quality, efficacy, and safety of the final product. For this reason, when a change is made to any of the elements involved in the manufacturing method (process), it is not possible to discuss the comparability of the product, i.e., its quality, efficacy, and safety, by assessing the comparability of the pre- and post-change elements alone or in terms of their general characteristics. The comparability of the final product after changing the element can be discussed only when process attributes and quality attributes in that element are linked to efficacy and safety and evaluated (as well as additional nonclinical and clinical studies as necessary) for given clinical indications of the target medical product (final product).

That is, the comparability of quality related to the efficacy of the final product can be demonstrated with no additional nonclinical or clinical studies only when major quality attributes liked to efficacy are thoroughly identified within the technically possible and scientifically reasonable scope and these quality attributes, including in vitro quantification, can be analyzed and evaluated. If it is difficult to evaluate the comparability of efficacy by in vitro studies alone, application to animal models or application to humans after setting up a clinical study should be utilized as appropriate. In addition, in order to demonstrate the comparability of safety by quality attributes without additional nonclinical or clinical studies, non-negligible risk factors apparently linked to an assumed serious safety risk (e.g., hazards such as the generation and mixing of malignant transformed cells that increase the risk of tumorigenesis after administration) must have been identified through a reasonable risk assessment and must be available for analysis and evaluation, for example, by detection or quantification by in vitro studies. If there are potential hazards that can be assumed but the relationship to serious risks in humans is unclear, or if hazards that can be clearly linked to serious risks in humans cannot be analyzed and evaluated in an in vitro study, it will be necessary to consider a new application to animals (or an animal model, if necessary) to observe whether there are differences in the way abnormalities occur before and after the process change, i.e., it is necessary to determine whether the presence of a risk-inducing hazard is at least comparable from the safety perspective on an animal level.[8]

However, this shall not apply in cases where it can be explained that, based on various knowledge, changes to the elements (quality of raw materials, manufacturing-related materials, or intermediate products, and manufacturing processes) do not adversely affect the quality attributes and other parameters of the final product (see the assumed outcomes (A) and (B) in Section "1.4.1 General Principles"). For human cell-processed products using cells collected from patients, the comparability assessment using the final product may not always be appropriate. In other words, for products that use autologous cells obtained from patients as starting materials that are then returned to the patients after minimal processing, such as concentration and sheeting, individual differences among patients may have a greater impact on quality attributes or efficacy/safety than changes associated with the process change. In such cases, substantially clearer assessment may be possible by evaluating the impact on limited parameters associated with the change to a reasonable extent depending on the degree of processing or change, target disease, and other factors, rather than conducting extensive analyses or nonclinical studies using the final product to collect highly variable data. However, even in such cases, it is still necessary to demonstrate that the change to the manufacturing process does not have unwanted effects on the efficacy and safety of the product. It should also be noted that autologous products can be evaluated using model cells.

2.0 Guidelines

2.1 Considerations for Comparability Exercise

[8] When considering implementing an animal study, it should be noted that human-derived specimens are valuable, that there are limitations in evaluating the safety and efficacy of a human-derived product in clinical settings using an animal study, and that the number of animals used should be reduced as much as possible according to the 3R principle (replacement/reduction/refinement) by employing an alternative method without using animals or by utilizing clinical data.

The goal of a comparability exercise is to confirm that the pre- and post-change final products are comparable in terms of quality, efficacy, and safety. To meet this goal, the products should be evaluated at the process step most appropriate for detecting a change in the critical quality attributes in particular. This may inevitably entail evaluating the target cells and product at multiple stages of manufacturing. For example, even when a process change is made only in the manufacturing process of the target cells, it would be appropriate to collect data on both the target cells and the final product in order to establish comparability if it is not possible to clearly explain that the change does not affect the critical quality attributes or other characteristics of the final product. In some cases, comparability between pre- and post-change products can be deduced from quality studies (with limited or extensive analysis, as appropriate), but there are cases where nonclinical or clinical comparability bridging studies may be required (for example, the case where an appropriate in vitro potency test cannot be set up and the comparability of the potency cannot be demonstrated). The extent to which testing to demonstrate comparability should be conducted depends on the following:

(A) The potential impact of the changes on the purity as well as on the physicochemical and biological properties of the product, particularly considering the complexity and degree of knowledge of the product (e.g., impurities, product- related substances);

(B) The availability of suitable analytical techniques to detect potential product modifications and the results of these studies; and

(C) The relationship between quality attributes and efficacy/safety, based on nonclinical and clinical experience and relevant information and data.

When considering the comparability of products, the manufacturer should evaluate, for example, the following:

(a) Relevant physicochemical and biological characterization data regarding quality attributes;

(b) Results from analysis of relevant samples (e.g., intermediate products, target cells, and final product) from the appropriate stages of the manufacturing process (e.g., possible differences between the target cells and non-target cells that could be a hazard);

(c) Batches used for proving the constant reproducibility of manufacturing;

(d) Accumulated batch data showing insights into the relationship between variations in quality attributes and efficacy/safety noted following single or multiple process change(s) in the past. That is, the manufacturer should consider the impact of changes over time to confirm that an unacceptable impact on safety and efficacy profiles has not occurred.; and

(e) Necessity of exploring the scope of manufacturing conditions, including stress conditions, to obtain information on possible differences among products due to alteration or degeneration of the cells or secretory factors (specifically, differentiation, purity, aging, and other conditions of the cells, possible differences in secretory factors and non-target cells).

In addition to evaluating the above data, the manufacturer should also consider the following:

(f) Necessity of exploring and measuring new variable factors or new quality attribute indicators to understand the impact of the process change on the efficacy, safety, and quality of the final product;

(g) Critical control points in the manufacturing process that affect product characteristics:

For example, presence or absence of downstream processes (e.g., separation of target cells by flow cytometry) that can appropriately process the cells manufactured by the changed manufacturing process, and if present, effects of the change on the quality of products in the downstream processes;

(h) Adequacy of the in-process controls including critical control points and in-process testing:
In-process controls for the post-change process should be confirmed, modified, or newly created, as appropriate, to ensure and maintain the quality of the product; and

(i) Nonclinical or clinical characteristics of the final product and its clinically indicated diseases (see Section 2.5 “Nonclinical and Clinical Considerations”).

2.2 Quality Considerations

2.2.1 Analytical Techniques

The battery of tests for the comparability exercise should be carefully selected and optimized to maximize the potential for detecting relevant differences in the quality attributes of the product that might result from the proposed process change. To cover physicochemical and biological properties to the extent possible, the same quality attribute (e.g., expression or secretion of biomarkers in target or non-target cells contained in the final product, mixing ratio of target and non-target cells contained in the final product, abundance of harmful non-target cells present, abundance of non-cellular impurities present) should be evaluated using multiple analytical methods, if possible, to obtain more reliable results. In such cases, it is necessary to employ physicochemical/biological analysis methods, each based on different principles, to collect data on the same quality attribute parameter so that changes in the product caused by the process change can be detected to the greatest extent possible.

With a series of analytical techniques set up for the product before the process change, it may be difficult to detect changes in the product due to limitations of the analytical method (e.g., precision, specificity, and detection limits) and, for some products, due to increased complexity caused by the heterogeneity of the cells in the final product. Consequently, the manufacturer should determine the following:

(A) Whether or not existing tests remain appropriate for their intended use or should be modified. For example, if a process change alters the characteristics (e.g., proliferative potential) or cell strain composition of non-target cells that may pose a hazard as impurities, it should be confirmed that the tests used to detect or quantify and evaluate these potentially hazardous non-target cells are appropriate for their intended purpose. In some cases, it may be appropriate to partially modify existing tests to detect novel non-target cells.

(B) Necessity of adding new tests because changes in quality attributes cannot be measured with existing methods. In other words, it would be appropriate to develop a new analytical technique when it is reasonably anticipated that a process change (e.g., a change in raw materials or manufacturing-related materials, or a partial change in the cell expansion and culture process) could result in a significant change in the quality attributes of the final product that cannot be measured with existing methods. In such cases, it would be appropriate to use a new method that is superior to the analysis methods that have been used for characterization or existing routine tests (e.g., specification tests, in-process control tests).

In characterization, it is not always necessary to use validated measurement methods, but the methods to be used must be scientifically reasonable and capable of providing reliable results.

Measurement methods to be used for batch release testing should be validated in accordance with ICH guidelines (e.g., ICH Q2(R1), Q5C, and Q6B), as appropriate.

2.2.2 Characterization

Characterization of human cell-processed products using appropriate methods includes determination of product heterogeneity/complexity, potency (if possible), various cell functions (if applicable), immunological properties (if applicable), purity, impurities, contaminants, and quantities.

Usually, it is necessary to re-perform all or part of the characterization performed at the time of the application for approval (if part of the characterization is to be performed, its validity must be explained) in order to directly compare the pre- and post-change products and determine their comparability. In general, only limited quality attribute information may be obtained with the results of specification and characterization tests alone. In addition, if the characterization performed at the time of application for approval is not sufficient to determine the comparability, it is advisable to explore and identify new indicators and their utilization as necessary, while reviewing their validity as indicators of existing critical quality attributes once again. In some cases, it may be necessary to understand the relationship between process parameters or raw material quality and critical quality attributes, as well as to identify new factors of variation and perform an additional characterization. As a result, if the characterization profile obtained from the additional characterization of the product after the process change differs from the profile found in the product used for nonclinical and clinical studies or an appropriate and equivalent product (e.g., marketed batch), it is necessary to evaluate the implications of the difference. Rather than considering performing additional characterization when a change is made to the manufacturing process, it is useful for the subsequent comparability exercise to perform an extensive and in-depth characterization of the batches used in the pivotal clinical trial or batches manufactured by the same method to the extent possible in advance to collect information.

To perform the comparability exercise, it is necessary to consider the following elements as important points.

(A) Heterogeneity and Complexity of Cell Population

To assess the level of heterogeneity of a cell population, it should be ascertained whether the cell strain type in the product, as well as the attributes and characteristic indicators that characterize the cell strain, are appropriate in terms of efficacy and safety perspectives in the final product. An attempt should be made to confirm that the abundance of the target cell types (or effective cell strain) and non-target cell types (or non-target harmful cell types) has been maintained within the predetermined range in the product after the process change. If appropriate information on the efficacy mechanism of the target cell types is not available, it may be possible to demonstrate that the abundance of the target cell types is maintained within a predetermined range by measuring relevant biological properties or other characteristic indicators. If differences are observed in the abundance ratio of the target cells or the profile of non-target cells in the product before and after the process change, it is necessary to examine the impact of such differences on efficacy or safety. If novel non-target cells are detected, it is necessary to characterize these cells to the extent possible. Depending on the type and amount of non-target cells, it may be necessary to conduct a nonclinical or clinical study to ensure that there are no unwanted effects on the efficacy or safety of human cell-processed products.

(B) Potency

Potency assay can be utilized for various purposes in determining the quality attributes of a product. However, the mechanism of action is commonly unclear in human cell-processed products and thereby, in many cases, this results in difficulty setting in vitro/in vivo studies to predict and guarantee clinical efficacy. If possible,

setting up an appropriate potency assay is useful for characterization and batch analysis and, in some cases, could serve as a link to clinical activity. The manufacturer should recognize that due to the limitations of potency assay (e.g., high variability), changes resulting from a process change may not be detectable.

If a potency assay cannot be set up and is not considered sufficient or appropriate as a method to confirm that the efficacy of the final product has been maintained, it may be appropriate to conduct a nonclinical or clinical study in some cases. (See Section 1.4.2 “Basic Concepts for Comparability Exercise”)

Even if a change is made to the manufacturing process for human cell-processed products composed of human-derived cells with complex and dynamic characteristics, it is necessary to consider performing a series of functional tests designed to evaluate the potency of the product. For example, if a cell type that will be an active ingredient of the final product exerts its efficacy through multiple functions, consideration should be given to evaluating the relevant cell functions to the extent possible.

(C) Potential Critical Quality Attributes

If a correlation between the quality attributes of the product and its clinical efficacy or safety has not been adequately demonstrated, or if the mechanism of action has not been elucidated, i.e., if the quality attributes of the product are poorly defined as critical quality attributes and many of them have only a potential to be defined as such, the manufacturer needs to develop measures to reasonably demonstrate that the nonclinical or clinical action has not been compromised in the post-change product. For example, it is also possible for the manufacturer to confirm that the abundance of the target cell types in the post-change product has been maintained within a predetermined range and, based on past findings, explain that efficacy has not been compromised. (See Paragraph 2 of Section 1.4.2 “Basic Concepts”)

(D) Immunological Properties

If the properties as a target of immune response or a subject of action are part of the characterization (e.g., human immune cell-processed products), it is necessary to confirm that the pre- and post-change products are comparable in terms of its specific immunological properties.

(E) Non-cellular Impurities and Contaminants

It is necessary to select a combination of analytical methods that will provide data to determine if there is any change in the profile of non-cellular impurities or contaminants in the product. If any difference is observed in the profile of non-cellular impurities or contaminants in the product before and after the process change, it is necessary to examine the impact of the difference on efficacy or safety. If new non-cellular impurities or contaminants are detected, it is necessary to characterize these to the extent possible. Depending on the type and amount of non-cellular impurities or contaminants, it may be necessary to conduct a nonclinical or clinical study to ensure that there are no unwanted effects on the efficacy or safety of human cell-processed products.

Contamination with infectious agents or other contaminants should be strictly avoided. If necessary, contamination should be properly controlled by in-process acceptance criteria or action limits for manufacturing the target cells or final product. If any new contaminants are detected after the process change, it is necessary to evaluate or examine the effects on the quality and efficacy/safety of the product.

2.2.3 Specifications

The existing test items and analytical methods of specifications for the target cells and final

product alone are usually considered insufficient to determine the effects of process changes. This is because they are selected for the purpose of checking the quality of each product manufactured, rather than for fully analyzing the characteristics of the product. The manufacturer should confirm that the specifications after the process change are appropriate to ensure the quality of the product. If the obtained results show a deviating trend from historical manufacturing data although the results meet the acceptance criteria, it may be necessary to conduct an additional study or analysis, as a change may have occurred to the product. If obtained data or information indicate that the test set up before the process change is no longer appropriate for the constant batch analysis of the post-change product, it is necessary to consider the necessity of changing or deleting the test or adding a new test. For example, if bovine serum is excluded from the cell culture process, the tests associated with bovine serum will no longer be necessary. On the other hand, it is generally deemed inappropriate to broaden the acceptance criteria unless there is a justifiable reason to do so. If the non-target cell profiles or non-cellular impurity profile changes after a process change and a relatively large amount of new impurity is present, it may be appropriate to set up specifications for this impurity. In setting up specifications for the post-change product, it is important to consider the general principles for setting up specifications specified in the ICH Q6B guideline; i.e., validated manufacturing process, characterization, batch analysis data, stability data, and nonclinical and clinical study data.

2.2.4 Stability of final Product Quality

When any changes are made to the manufacturing process of the target cells, even if they are minor changes, they may affect the stability of the quality of the final product after the change. For any change to the manufacturing process that may alter the characteristics or abundance of the target/non-target cell profiles, or non-cellular impurity profile, its effect on the stability of the product should be evaluated. The stability of the final product may be affected by changes to the material cells or to the culture conditions, washing, physical treatment, storage temperature, or cell cryopreservation solution. Therefore, in general, for products that may be affected by a process change, stability testing should be initiated with the actual storage time and temperature as appropriate following the process change.

Accelerated and stress stability studies with an assumption of environmental worsening due to vibration, temperature, and other factors during transportation or storage can be useful tools that enable direct comparison of transportation and storage stability of the pre- and post-change products; therefore, consideration should be given to their feasibility and necessity. The results obtained through these studies may be suggestive of changes in the product that warrant additional evaluation. The results may also provide a basis for judgment regarding the need to set up additional items to be controlled during the manufacturing process as well as during transportation and storage to eliminate unintended changes. It is necessary to perform appropriate reviews to ensure that the selected storage conditions and control items are appropriate.

Conditions for stability studies that provide data to be compared before and after the process change should be set up with reference to the ICH Q5C and Q1A(R2) guidelines.

2.3 Manufacturing Process Considerations

To consistently manufacture products meeting the acceptance criteria, it is necessary to strictly define the manufacturing process, including various in-process controls, and to maintain its consistency. Whatever the manufacturing process change is, the measures to evaluate its impact vary depending on the knowledge and experience of the manufacturer in terms of the relevant process, product, and manufacturing process, as well as the data obtained during the development process. The manufacturer must ensure that the in-process control after the process change can assure the quality of the product as effectively as or more effectively than the in-process control before the

change.

It is very important to carefully examine the impact of the planned process change on the steps downstream and the quality attributes associated with each of those steps (e.g., effects on the acceptance criteria, in-process specifications, in-process control tests, operating limits and, if applicable, essential process parameters and other characterization items). Such an examination will help identify which tests should be performed during the comparability exercise, which in-process or batch release acceptance criteria or analytical procedures should be re-evaluated, and which steps will be less affected by the process change. If analysis of intermediate products during the manufacturing process suggests that some changes will occur in the final product, it may be necessary to evaluate the adequacy of existing test methods to detect such changes. If some steps in the manufacturing process are to be excluded from the above examination, it is necessary to demonstrate the validity of such exclusion.

When the relevant in-process control is re-set following a process change, it is necessary to confirm that the pre- and post-change final products under the new in-process control are comparable. To demonstrate comparability, it is often useful to demonstrate, for example, that particular intermediate products are comparable, or that the changed process is capable of eliminating harmful non-target cells and process-derived non-cellular harmful impurities (including those newly generated by the manufacturing process change) to an appropriate level. The validity of a process change for an approved product is usually demonstrated by data obtained from batches manufactured at the commercial scale.

The manufacturing process should be assessed in consideration of factors such as the criticality of the process step, location of the change and potential effects on other process steps, and the type and extent of change. Useful information for this assessment is generally available from several sources. Examples of such information sources include the following: knowledge gained during the course of setting up process steps; results of small-scale evaluation, validation, or verification of process steps; experience with previous process changes; experience with facilities in similar operations; similar process changes with similar products; and literature. Although information from external sources is useful to some extent, it is limited to information related to the specific manufacturing process and specific product subject to the assessment of a process change.

When any change is made to the manufacturing process (including all new control items), it is necessary to assure that the changed process can also manufacture comparable products through coordination of in-process controls. The changed process steps should be subject to process verification or process validation/assessment again, as necessary. The in-process controls, including critical control points and in-process control tests, should ensure that the changed process is adequately controlled and that the quality of the product has been ensured and maintained. Usually, if it can be judged that the performance of subsequent (downstream) process steps will not be affected, or the quality of intermediate products obtained through subsequent process steps will not be affected based on experience with historical production batches, performance data, clinical data, or technical considerations, it is deemed unnecessary to perform additional process verification or process validation/assessment. If the change is expected to affect more than one process step, it may be appropriate to perform a more extensive analysis on the process change, followed by a subsequent verification or process validation/assessment.

The state of control over the changed process can be demonstrated by actions including, but not limited to, the following:

- Establishment of changed specifications for starting material cells and other raw materials, materials, and manufacturing-related materials (ancillary materials);

- Assessment of the viral safety of changed cells following changes to the cell lines or cell banks as the starting materials for production;

- Adventitious agent testing and control;
- Elimination of harmful target cell-derived impurities, and harmful non-target cells and process-related impurities; and
- Maintenance of the purity level.

Even when a change is made to the manufacturing process of approved products, the appropriate number of batches manufactured after the change should be analyzed to demonstrate the constant reproducibility of the process.

To facilitate analysis of the process change and control measures, the manufacturer should summarize information related to the manufacturing process before and after the change, and prepare an explanatory document in a side-by-side format that enables clear understanding of the change details in the manufacturing process and control testing.

2.4 Comparability Following Process Changes during Development

During the development phase, it is expected that various changes will be made to the manufacturing process that may affect the quality, efficacy, and safety of the final product. The comparability exercise is usually performed to transfer nonclinical and clinical study data obtained from the human cell-processed products before the process change to the human cell-processed products after the change, to facilitate subsequent development, and ultimately to help obtain approval for the final product. Factors affecting the comparability exercise for human cell-processed products under development include the stage of product development at which the manufacturing process is changed, the extent to which validated analytical methods are available, and the level of knowledge about the product and the manufacturing process. The degree to which these factors should be considered depends on the level of experience the manufacturer has in the process.

If process changes are made during the development phase before nonclinical studies, issues of comparability assessment will generally not arise. This is because nonclinical and clinical studies will be conducted using the post-change product as the manufacturer proceeds with continuing development. When making process changes during early phases of nonclinical and clinical studies, it should be decided whether or not to perform comparability exercises, taking into consideration the necessity of the data as materials to be submitted for approval, the content, quality and significance of the data to be obtained, and other factors. Also, the appropriate manner should be chosen by considering time, labor, costs, and other factors that can be used for the research and development.[9] As knowledge and information accumulates and development of analytical methods progresses, comparability exercises can generally be made broader and richer in terms of both content and quality by utilizing such information, but the data to be obtained are only for the comparability assessment for the old and new products during development. It should be noted that, in contrast, the approval review is based on evaluation of the quality, efficacy, and safety of the final product by the manufacturing process finally selected for marketing authorization. If a process change is made in the late phase of development, but no additional clinical studies are planned to support marketing authorization, the comparability exercise should be performed before and after the process change as extensively and thoroughly as when a change is made to the manufacturing process for the approved product. Depending on the results of comparability studies on quality attributes, additional nonclinical or clinical studies may be required.

When performing a comparability exercise during the development phase, it is necessary to use

[9] For human cell-processed products, the relationship between the data obtained through, for example, potency studies and clinical efficacy is not always clear at these phases. On the other hand, for quality attributes that are clearly related to safety or directly linked to serious harm, such as the presence of infectious agents that can cause serious diseases, a comparability assessment similar to that required for changes to the manufacturing process of an approved product is required.

appropriate assessment techniques. Although analytical methods may not always be validated during the development phase, test methods and data must always be scientifically valid as well as reliable and reproducible.

2.5 Nonclinical and Clinical Considerations

2.5.1 Factors to Be Considered in Planning Nonclinical and Clinical Studies

Comparability of human cell-processed products before and after a process change can be established solely on the basis of the quality considerations outlined in this document by the manufacturer, if comparability can be assured with these considerations (see Section "2.2 Quality Considerations"). If comparability cannot be confirmed by data on quality, it should be demonstrated by additional nonclinical or clinical studies. The extent and details of nonclinical and clinical studies for the comparability exercise will be determined on a case-by-case basis, taking into account various factors including the following:

(A) Quality Findings

- Final product – The type, nature, and extent of differences between the pre- and post-change products with respect to quality attributes of the target cells, non-target cells, process-related non-cellular impurities, and additives. For example, new impurities may require toxicity testing to determine whether their presence and amount are acceptable;

- Results of the verification or process validation/evaluation on the new process including the results of relevant in-process control tests; and

- Universality (including usefulness and availability/accessibility) of the test method used in the comparability assessment, and its capabilities/qualifications and limitations as a test method.

(B) Type/Characteristics and Knowledge Level of Product

- Product complexity including heterogeneity of cell populations: Physicochemical and in vitro/in vivo assays on biological properties may not be able to detect all quality differences attributed to heterogeneity of cell populations;

- The stronger the association between quality attributes and efficacy/safety, the more likely it is to show comparability.

- Comparability should be examined for interactions between the target or non-target cells and the cells of the patient (recipient), immune response induced by the target or non-target cells, and immunogenicity due to process-related non-cellular impurities or additives; and

- The more known and clear the mechanism of action is, the more likely it is to show comparability.

(C) Existing Nonclinical and Clinical Data Relevant to the Product, Aspects of Product Use, and Human Cell-processed Product Type

- Indications/target patient groups: The impact of possible differences between the products can vary between the target patient groups (e.g., risks for unintended immune response induced by the target or non-target cells or unintended

immunogenicity due to process-related impurities). It may be appropriate to consider the consequences separately for each indication;

- Dosing regimen and route of administration, etc.: The risk of certain possible consequences of a difference between the products, such as unintended immune response induced by the target or non-target cells or unintended immunogenicity due to process-related impurities, could be increased further with long-term administration compared with short-term administration;

- Past experience (e.g., safety associated with immune response and immunogenicity): Experience with existing cell-processed products, especially with rare adverse effects (e.g., in situations of immune response induction) can be helpful;

- Relationship between kinetics or biodistribution of human cell-processed product in the nonclinical development phase and nonclinical or clinical data on supporting efficacy; and

- Relationship between kinetics or biodistribution of human cell-processed product in clinical use and efficacy or safety data of the product.

2.5.2 Type of Studies

The nonclinical and clinical studies referred to in this document might include, depending on the situation, kinetic studies, biodistribution studies, nonclinical efficacy studies, various safety studies, immunogenicity studies, or clinical studies (including phase 4 clinical studies [post-marketing clinical studies] on efficacy and safety). The purpose of these studies is to contribute to the assessment of comparability of the products before and after a change to the manufacturing process. These studies may be appropriate as direct comparability assessments in some cases.

3.0 GLOSSARY

Starting Material

According to ICH Q3 guideline, starting material is defined as "A material used in the synthesis of a new drug substance that is incorporated as an element into the structure of an intermediate and/or of the new drug substance." In the manufacture of human cell-processed products as described in this guideline, it refers to "a material used in the manufacturing of a target cells and incorporated into an intermediate product, the target cells or the cell from which the final product is derived or the structure of these cells (e.g., a gene vector used for gene transfer into the cell from which the final product is derived)."

Comparability Exercise

A series of activities, including study design, study implementation, and data evaluation, that are designed to investigate whether or not the products are comparable.

Comparability Bridging Study

A nonclinical or clinical study designed to make existing data from human cell-processed products manufactured by the current manufacturing process available for human cell-processed products to be manufactured by the changed manufacturing process.

Comparable

The conclusion that human cell-processed products before and after the manufacturing process change are highly similar in terms of quality attributes and that no unwanted effects have occurred on the safety or efficacy of the human cell-processed products. Because many human cell-processed products have complex and heterogeneous populations of material cells and

processed cell components, and the mechanism of action is not always completely clear, it may be necessary to assess comparability based not only on analysis of the specifications and quality attributes of the final product, but also on the data from nonclinical and clinical studies conducted as needed.

Hazard(s)

Potential source of harm (ICH Q9 guideline, ISO/IEC Guide 51). For a hazard that has already been assessed for risks to humans and animals and has been associated with harm, it is expected that the risks associated with the hazard can be avoided or reduced by avoiding or reducing the hazard to the extent technically possible and scientifically reasonable. In contrast, for a hazard that can be assumed but is not clearly associated with harm in humans or animals, it is necessary to consider applying the final product or target cells to animals (or animal models, if necessary) and observing whether or not there is any possibility of the assumed harm occurring, i.e., whether the existence of any hazard with an unclear association with the risk can be determined to be acceptable at least in animals in terms of safety.

Critical Quality Attribute

A quality attribute that is essential for assuring product efficacy or safety and the product quality required for guaranteeing efficacy and safety. However, for some human cell-processed products, it may not be possible to identify or measure their critical quality attributes with the technology available at the time.

Quality Attribute

A molecular, cellular, or product characteristic that is selected as appropriate to describe the quality of the product, and is specified in conjunction with the identity, purity, potency, stability of the product, safety of adventitious agents, and other factors. Specifications evaluate a selected subset of the quality attributes. For human cell-processed products, not only attributes of the cell itself, but also parameters of the cell supernatant during the manufacturing process (e.g., analyzed values of metabolites or components such as extracellular vesicles) and the shape of the final product (e.g., sheet-like or specific three-dimensional structure) may also be important as quality attributes.

Non-target Cells

Any cell in the final product other than the target cells. Non-target cells that can be hazards (non-target harmful cells) include residual undifferentiated pluripotent stem cells, growth-defective transformants, and cells abnormally excreting cytokines. Non-target cells that do not constitute a hazard are not impurities. See “Points to Consider on Undifferentiated Pluripotent Stem Cells/Transformants Detection Testing, Tumorigenicity Studies, and Genetic Stability Assessment for Human Cell-processed Products” (Annex of Notification No. 0627-1 of the Medical Device Evaluation Division [MDED], Pharmaceutical Safety and Environmental Health Bureau [PSEHB] dated June 27, 2019) for how to detect residual undifferentiated pluripotent stem cells and growth-defective transformants.

Target Cells

A cell contained in the final product as an active ingredient or a cell assumed to be an active ingredient in the final product.

4.0 REFERENCES

Stability Testing of New Drug Substances and Products (ICH Q1A(R2)) (Annex of PFSB/ELD Notification No. 0603001 dated June 3, 2003).

Validation of Analytical Procedures: Text and Methodology (ICH Q2(R1)) (Attachment of PMSB/ELD Notification No. 338 dated October 28, 1997).

Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin (ICH Q5A(R1)) (Annex of PMSB/ELD Notification No. 329 dated February 22, 2000).

Stability Testing of Biotechnological/Biological Products (ICH Q5C) (Attachment of PMSB/ELD Notification No. 6 dated January 6, 1998).

Derivation and Characterisation of Cell Substrates Used for Production of Biotechnological/Biological Products (ICH Q5D) (Annex of PMSB/ELD Notification No. 873 dated July 14, 2000).

Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process (ICH Q5E) (Annex of PFSB/ELD Notification No. 0426001 dated April 26, 2005).

Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products (ICH Q6B) (Annex of PMSB/ELD Notification No. 571 dated May 1, 2001).

Quality Risk Management (ICH Q9) (Annex of PFSB/ELD Notification No. 0901004 and PFSB/CND Notification No. 0901005 dated September 1, 2006)

Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management (ICH Q12) (Annex of PSEHB/PED Notification No. 1029-1 and PSEHB/CND Notification No. 1029-1 dated October 29, 2021)

Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals (ICH S6(R1)) (Annex of PFSB/ELD Notification No. 0323-1 dated March 23, 2012).

Statistical Principles for Clinical Trials (ICH E9) (Annex of PMSB/ELD Notification No. 1047 dated November 30, 1998).

Choice of Control Group and Related Issues in Clinical Trials (ICH E10) (Annex of PMSB/ELD Notification No. 136 dated February 27, 2001).

Appended Table 2 (Related to Article 1-2) of the Cabinet Order on the Development of Related Cabinet Orders and Transitional Measures Accompanying the Enforcement of the Act for Partial Amendment of the Pharmaceutical Affairs Act, etc. (Cabinet Order No. 269, 2014).

Ministerial Ordinance on the Good Gene, Cellular, and Tissue-based Products Manufacturing Practice (GCTP) for Regenerative Medical Products (MHLW Ministerial Ordinances No. 93, 2014).

Points to Consider on Undifferentiated Pluripotent Stem Cells/Transformants Detection Testing, Tumorigenicity Studies, and Genetic Stability Assessment for Human Cell-processed Products (Annex of PSEHB/MDED Notification No. 0627-1 dated June 27, 2019).

Questions and Answers (Q&A) on the Guideline for Comparability of Human Cell-Processed Products Subject to Changes in Their Manufacturing Process

Page, Line	Guideline section/subsection	Question	Answer
p.3, L46	1.4 General Principles	Show us some examples with respect to: "(A) On the basis of the comparison of relevant quality attributes to the extent technically possible and scientifically reasonable in light of the current state of science and technology, the pre- and post-change products are highly similar and the change does not affect quality attributes that are essential for ensuring the efficacy and safety of the product (critical quality attributes), i.e., the products are considered to be comparable and are not likely to have an adverse effect on efficacy and safety. "	For example, there might be an applicable case where a manufacturer of non-cellular manufacturing-related materials, such as low-molecular-weight-compound raw materials or materials, is changed.
p.4, L3	1.4 General Principles	Show us some examples with respect to: "(C) If the pre- and post-change products appear to be highly similar, but changes that could affect the efficacy and safety of the product cannot be adequately identified by the analytical method used, consideration should be given to conducting additional quality studies (e.g., characterization) or nonclinical or clinical studies in order to draw definitive conclusions."	For example, there might be an applicable case where a differentiation-inducing or culturing method of the cells is changed. Anyway, a criterion for conducting additional testing or re-testing is whether or not it is possible to perform cell characterization that enables us to discuss the correlation between efficacy and safety. In terms of quality, it is limited to cases where the pre- and post-change comparability (as well as the appropriateness of additional characterization) can be assessed at the level of the active ingredient cell. When a cell differentiation-inducing or culturing method is changed, cell quality attributes are highly likely to change and thereby additional characterization should more likely be an effective method that links to efficacy and safety, and a series of new nonclinical or clinical studies are more likely to be required. When another nonclinical or clinical study is to be conducted, it may be more

			reasonable to use the data already obtained as reference material and aim for marketing approval as a new product based on the new nonclinical or clinical study.
p.4, L9	1.4 General Principles	Show us some examples with respect to: "(D) Although the pre- and post-change products appear to be highly similar, differences are identified through comparison of the quality attributes of the products, and it cannot be ruled out that there may be unwanted effects on efficacy and safety. In such cases, it is considered inadequate to determine that the pre- and post-change products are comparable simply by collecting and analyzing additional data on the quality attributes. Therefore, consideration should be given to conducting nonclinical and clinical studies to a certain extent[7] for the assessment of comparability."	For example, there might be an applicable case where the master cell bank of human pluripotent stem cells as materials is changed for the manufacturing of human pluripotent stem cell-processed products, and that you have poor clinical experience in similar products. When another nonclinical or clinical study is to be conducted, it may be more reasonable to use the data already obtained as reference material and aim for marketing approval as a new product based on the new nonclinical or clinical study.
p.4, L30	1.4 General Principles	As for the statement "even if all quality attributes measurable with current technology are listed for human cell-processed products, it may not always be assured that all critical quality attributes necessary to fully assure the comparability of efficacy and safety have been completely covered and identified," what differences are expected to occur between the "comparability" for biotechnological products and that for cell-processed products?	In the meaning of "it may not always be assured that all original and critical quality attributes... have been completely covered and identified." it is likely that most human cell-processed products fall under category (D) "Not non-similar" rather than categories (A) to (C) as defined in the "comparability" assessment cases for conventional pharmaceuticals or biotechnological products. Anyway, considering that there are still few case examples of scientifically established efficacy or safety even in approved products, including products subject to post-marketing monitoring, and that the relationship between their efficacy or safety and their quality attributes has not necessarily been elucidated, we must say that the concepts and measures are not yet mature enough to discuss the

			comparability of human cell-processed products in completely the same sense as the comparability for low-molecular-weight pharmaceuticals or that specified in ICH Q5E guideline. Therefore, when the comparability of the pre- and post-change final products cannot be explained adequately with the quality attributes obtained through in vitro studies, consideration should be given to conducting additional studies on new quality attributes or nonclinical in animals or clinical studies.
p.6, L13	1.4 General Principles	What does it mean by "thoroughly?"	The term "thoroughly" does not mean pursuing studies endlessly, but it means, as described, that "serious and non-negligible" hazards should be identified "within the technically possible and scientifically reasonable scope at the time."
p.9, L40	2.2 Quality Considerations 2.2.2 Characterization (A) Heterogeneity and Complexity of Cell Population	Show us some examples with respect to: "If appropriate information on the efficacy mechanism of the target cell types is not available, it may be possible to demonstrate that the abundance of the target cell types is maintained within a predetermined range by measuring relevant biological properties or other characteristic indicators."	There might be a case where the expression of a specific surface antigen marker is known to correlate with efficacy based on cumulative scientific knowledge to date, such as clinical experience, even if the causal relationship with efficacy is unclear.
p.14, L35	2.5 Nonclinical and Clinical Considerations 2.5.1 Factors to Be Considered in Planning Nonclinical and Clinical Studies (B) Type/Characteristics and Knowledge Level of Product	Show us some examples with respect to: "Product complexity including heterogeneity of cell populations: Physicochemical and in vitro/in vivo assays on biological properties may not be able to detect all quality differences attributed to heterogeneity of cell populations."	This means that, for example, if the active ingredient cell is a heterogeneous cell population, it is difficult to detect all differences in quality between the pre- and post-change cell products. Furthermore, this means that attention should be paid when contamination of a hazard, such as a small amount of cells with tumorigenicity, is assumed to follow Poisson or other similar statistical distributions and when, moreover, the hazard is assumed to show proliferation at various levels.