Guideline Registration No.
Guideline-1444-02

Guideline on Comparability Assessment of Investigational Cell and Gene Therapy Products (Guidance for Applicants)

May 2026

MINISTRY OF FOOD AND DRUG SAFETY
National Institute
of Food and Drug Safety Evalution

Biopharmaceuticals and Herbal Medicine Evaluation Department

Cell and Gene Therapy Product Division

Document History

Guideline on Comparability Assessment of Investigational Cell and Gene Therapy Products (Guidance for Applicants)

Document No.	Endorsement	Details
Guideline-1444-01	September 24, 2025	Original Publication(Korean)
Guideline-1444-02	May 13, 2026	English version publication

Table of Contents

1. Introduction

1.1. Overview

Advanced biological products[1] are medicinal products manufactured through multi-step, complex procedures using various biological raw materials. They contain living cells, genetically modified viruses, or cells in which genetic material has been altered or introduced, as active ingredients. Furthermore, as the drug product may consist of heterogeneous cell populations, it possesses high inherent variability and complex biological characteristics.

These products face significant quality control challenges due to inherent factors such as limited knowledge of quality attributes and manufacturing experience, restricted and variable starting materials, small-scale production, and short shelf life.

Nevertheless, manufacturing processes or analytical methods are often modified during development to enhance quality, scale up manufacturing, and improve production efficiency. In such cases, it is critical to understand how these process changes would affect product quality.

The purpose of comparability assessment is to ensure the quality, safety, and efficacy of the drug product manufactured after process changes, and to confirm that such changes do not have an adverse impact on the drug product. When only nonclinical data are submitted for the initial clinical trial application, it should be demonstrated that the investigational product is comparable to the material used in nonclinical studies in terms of quality and safety. During the clinical stage if manufacturing changes occur, comparability between the pre- and post-change investigational products should be ensured by conducting comparability studies. Ultimately, at the marketing authorization stage, comparability should be demonstrated between the investigational product and the product intended for marketing authorization. During early clinical development, the comparability assessment should focus intensively on safety-related attributes. Appropriate comparability assessment strategy should be established as the product progresses through exploratory and confirmatory clinical trials.

[1] Cell therapy products and gene therapy products, which are referred to as advanced therapy medicinal products (ATMP), cell and gene therapy (CGT), etc. by the ICH and foreign regulatory agencies, are designated as "Advanced biological products" under South Korea's 「Act on the Safety of and Support for Advanced Regenerative Medicine and Advanced Biological Products」.

Comparability does not imply that the quality attributes of pre-change and post-change products are identical. Instead, comparability demonstrates that the products are highly similar and that any differences in quality attributes do not adversely affect the safety and efficacy of the products. Therefore, the safety and efficacy of the drug product are assessed by combining product characterization (via physicochemical or biological tests), analysis of manufacturing process elements, and, where necessary, non-clinical and clinical data. Consequently, if changes in quality attributes are identified, then the comparability assessment may require a combination of non-clinical or clinical studies in addition to analytical assessment of the quality attributes.

To determine the impact of changes in manufacturing (processes) and quality controls, it is necessary to carefully review all predictable consequences of the changes. To this end, comparability acceptance criteria should be established to determine high similarity between pre- and post-change products—specifically, criteria sufficient to ensure that existing information confirms that there are no negative impacts on the safety and efficacy of the drug product. Generally, comparability is assessed through a comprehensive comparison of all quality control data before and after the process change, including batch release testing, in-process controls (IPC), process suitability assessment process validation, characterization, and stability testing results. The comparability of the products before and after the change is objectively assessed by reviewing these results against pre-defined comparability acceptance criteria. It is useful to prioritize the quality attributes serving as the basis for comparability determination by considering their relevance to safety and efficacy and the significance of their impact. Critical Quality Attributes (CQAs)[2], which are closely linked to the safety and efficacy of the drug product, are essential elements to be assessed.

This guideline outlines basic considerations for comparability assessment when changes to manufacturing processes occur during the development of cell and gene therapy products (hereinafter referred to as "advanced biopharmaceuticals"[3]). It also describes the data and information required—focusing on quality control—to demonstrate that manufacturing changes do not adversely affect the quality, safety, and efficacy of the drug product.

---

2 A Critical Quality Attribute (CQA) refers to a physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality. ("Regulation on the Good Manufacturing Practice (GMP) for Medicinal Products" [Annex 13] 14. v.)

3 This guideline does not apply to tissue engineering products or advanced combination biopharmaceuticals, aside from cell and gene therapy products.

1.2. Background

Although all available quality attributes measurable by current technology are considered, the diversity in types, characteristics, and indications of advanced biological products makes it difficult to clearly define representative CQAs that can guarantee comparability in safety and efficacy. These attributes may also vary by product. As scientific understanding advances and data accumulation continues in this field, changes may also occur for individual products or at various development stages. Therefore, a flexible approach may be taken when handling each case of manufacturing or testing for comparability assessment, based on a scientifically sound and well-reasoned rationale grounded in the basic concepts of this guideline.

1.3. Legal Basis and Scope of the Guideline

To obtain approval for clinical trial protocols for advanced biological products, data should be submitted following the preparation instructions, scope, and requirements for data submission specified in Article 24 of the "Regulation on Safety of Medicinal Products, etc." The details are stipulated in the "Regulation on Approval for IND Application of Medicinal Products" (MFDS Notification).

For advanced biological product to be marketed, marketing authorization is required in accordance with Article 23(2) and Article 27(1) of the "Act on Safety and Support for Advanced Regenerative Medicine and Advanced Biological Products.” The submission for marketing authorization should be prepared in the Common Technical Document (CTD) format in accordance with Article 6 (Preparation of Common Technical Documents) of the "Regulation on Review and Marketing Authorization of Advanced Biological Products.” The details regarding the review of manufacturing, marketing, and import authorization (including post-approval changes) for cell and gene therapy products are stipulated in the “Regulation on Review and Marketing Authorization of Advanced Biological Products.” Article 11 of this Notification defines the scope of the data submitted for variations to marketing authorizations. Detailed data requirements are specified in Article 14 (Data Requirements for Cell Therapy Products), Article 15 (Data Requirements for Gene Therapy Products), Article 16 (Data Requirements for Non-clinical Studies), and Article 17 (Review Standards for Non-clinical Study Data) of the document. For comparability assessment regarding

manufacturing method changes after marketing authorization, refer to the "Guideline on the Comparability of Biopharmaceuticals in Manufacturing Process Changes." For general considerations for the manufacturing and quality of advanced biological products, refer to the "Guideline on Quality Assessment of Gene Therapy Products," "Guideline on Quality Assessment of Investigational Cell and Gene Therapy Products," "Guideline on Release Tests for Cell Therapy Products", and "Guideline on Evaluation of Cell Banks for Cell Therapy Products."

This guideline applies to investigational cell therapy and gene therapy products. Specifically, it describes methods for assessing comparability when changes in the manufacturing process or other areas are introduced during product development. However, the core concepts of this guideline may be applied to post-approval manufacturing changes that may impact product quality. It may also serve as a reference for comparability assessment of other biopharmaceuticals derived from human cells, such as extracellular vesicles, even if they are not classified as advanced biological products. Generally, manufacturing process changes, implemented during the development stage and prior to non-clinical studies, are not subject to the comparability assessment described in this guideline.

2. Overview

2.1. General Principles for Change Control

Clarification of Cell Source and Cell Bank Establishment Prior to Process Development

It is advisable to conduct sufficient testing on cellular starting materials in the early stages of product development and to clearly define and establish relevant cell sources[4] and cell banks before developing the manufacturing process for batches used in clinical trials, thereby minimizing the potential for future changes. This is because, in later development stages, it is difficult to correlate the justification for changes with quality attributes and clinical safety and efficacy.

Risk-Based Approach

Given the difficulty of change control due to product complexity, it is recommended to implement a systematic approach that identifies, assesses, and analyzes potential risks to mitigate them effectively. Defining acceptance ranges for Critical Quality Attributes (CQAs) and establishing Critical Process Parameters (CPPs)[5] prior to changes can facilitate risk assessment and change control. For instance, if operating ranges are established for each manipulation step in cell culture, switching from a manual to an automated process may be easier. Generally, approaches involving more rigorous statistical analyses are required when the risk is high. Visual comparison methods, such as side-by-side analysis or dot plots, may be sufficient to characterize the impact of low-risk manufacturing changes without statistical analyses.

Extensive Manufacturing Changes in Late-stage Development

When extensive manufacturing changes are to be introduced immediately prior to marketing authorization, greater caution should be exercised in assessing the level of potential risks to product quality. Reliable and comprehensive data should be provided to demonstrate that the change does not negatively impact product quality. When the existing

4 It is recommended to secure donor eligibility test results (including medical and social history) and genetic analysis data, such as Short Tandem Repeat (STR) profiles of donor tissues.

5 "A Critical Process Parameter (CPP)" refers to a process parameter whose variability affects critical quality attributes and should be monitored or controlled to ensure that the process produces a product of the desired quality. ("Regulation on the Good Manufacturing Practice (GMP) for Medicinal Products" [Annex 13] 14. u.)

process validation no longer represents the process proposed for marketing authorization due to late-stage manufacturing changes, additional process assessment and process validation are necessary. Therefore, it is recommended to introduce major changes before initiating pivotal clinical trials intended to support marketing authorization, if possible.

In cases where a manufacturing change is planned without the conduct of a new clinical trial for marketing authorization, comparability assessments before and after the change should be performed with a scope and level of rigor at a level comparable to, or exceeding, that applied to post-approval manufacturing changes.

Changes Affecting Product Stability (e.g., Storage Conditions)

Changes to storage conditions may negatively affect stability, particularly for advanced biological products as they are often sensitive to storage and handling. Therefore, product stability should be thoroughly assessed when changes are made to the primary container closure system, dosage form, strength or concentration of the active ingredient, or transport conditions. Stability studies should focus on assessing quality attributes related to stability-indicating parameters. While accelerated stability studies are useful for confirming such quality attributes, it is appropriate to establish shelf life based on long-term stability study results. When changes that may adversely affect product stability are introduced in the late stages of product development, consideration should be given to the possibility that drug development may be delayed due to the need to generate long-term stability data.

Changes Affecting Product Quality

Changes that may affect product quality include modifications to the manufacturing site, raw materials, container closure systems, analytical methods, and storage/transport conditions. Such changes may unexpectedly alter product purity (e.g., process-related impurities, cell-derived impurities associated with the active substance, increased aggregates or particulates), decrease stability, or alter potency. Any manufacturing site change is considered a major change that requires a more comprehensive comparability assessment than technology transfer. As this involves changes to manufacturing processes, transportation, manufacturing equipment and facilities (including test facilities and instruments), and personnel, the assessment for a site change should be conducted thoroughly, including comparability assessment of analytical methods as well as evaluation of CPPs.

Changes Expected to Have No or Minimal Impact on Product Quality

Changes classified as "Minor Quality Changes of Investigational Biological Products" in [Appendix 5] of the "Guideline on Quality of Investigational Medicinal Products"—which generally have low impact on subject safety and reliability of clinical trial outcomes —do not require separate extensive comparability studies or prior approval for the change. However, the sponsor should obtain data demonstrating that there is no or minimal impact on product quality or clinical outcomes, and such data should be included in the submission package for a subsequent clinical trial phase or in the dossier submitted for marketing authorization. For changes, other than those listed, that are considered to have a minimal impact on product quality, it is advisable to discuss the need for the conduct of comparability assessment through pre-consultation with the MFDS.

Cases Involving Multiple Changes

While multiple changes may be implemented simultaneously and assessed at once, failure to demonstrate comparability may make it difficult to identify root causes. Therefore, it is appropriate to implement and assess each change sequentially (establishing comparability for analytical method changes prior to manufacturing process changes, including a site change).

Considering that investigational products are at a stage where overall quality elements have not yet been fully established, including manufacturing processes, it is possible, based on a risk-based approach, to establish comparability for each individual change using small-scale batches, and, subsequently, to introduce multiple changes simultaneously and confirm final comparability using batches manufactured in compliance with applicable GMP requirements. For details, refer to the "Manufacturing Scale" section in "2.2 General Principles of Comparability Assessment."

2.2. General Principles of Comparability Assessment

Various changes to manufacturing process may occur during development, potentially affecting the quality, efficacy, and safety of the drug product. To apply the nonclinical and clinical data generated using the pre-change product as evidence to support the safety and efficacy of the post-change product for a future marketing authorization application, comparability should be confirmed between the pre- and post-change products. The comparability assessment that is conducted during development must employ scientifically valid, reliable, and reproducible methods.

For autologous cell-based therapies, variability in patient starting materials may have a greater impact on quality attributes, safety, and efficacy than changes to the manufacturing process. In such cases, comparability assessment using the final drug product may not be appropriate, and comparability may instead be demonstrated based on results from appropriate intermediate stages.

For autologous products, assessment using surrogate cells may be considered. However, it must still be demonstrated that the change does not adversely affect the safety and efficacy of the products.

Comparability assessment requires careful selection of product quality attributes, analytical methods, acceptance criteria, and statistical methods. It is recommended that a detailed comparability assessment plan, including statistical approaches, be prepared and discussed with the MFDS prior to conducting the study. The scope of the comparability study should be determined via risk assessment. This includes defining in advance: 1) key quality attributes to be assessed; 2) appropriate analytical methods to be used; and 3) comparability acceptance criteria suitable for demonstrating the absence of adverse impacts on product quality. To assess comparability following changes, it is common to assess quality attributes (characteristics) that were not included in batch release testing.

Strategy for Quality Attribute Investigation and Comparability Assessment

Due to the inherent complexity of the biological characteristics of advanced biological products, there are limitations in comprehensively characterizing quality attributes of the active substance at the molecular level. Therefore, a more holistic quality assessment focusing on functional or biological activity is required. For cell therapy products, it is also necessary to characterize cell populations (composition) and to analyze physiological and

biological changes driven by environmental factors (e.g., differentiation or dedifferentiation), as well as cellular responses to the environment (e.g., cytokine release).

It is important to define technically measurable quality attributes and assess comparability based on those attributes. When changes are made to cell lines or cell banks used as starting materials for cell therapy products, comparability of the drug product with respect to safety and efficacy-or of the quality attributes that ensure safety and efficacy-should first be established, as this may be a prerequisite for assessing the comparability of the cell lines or cell banks. Demonstrating the absence of differences in general cellular characteristics or safety-related parameters alone is not sufficient to establish comparability of the drug product in terms of quality attributes or nonclinical and clinical outcomes. Since most cell-based therapies consist of heterogeneous cell populations and available analytical methods have inherent limitations, it is difficult to fully capture and assess cell subpopulation (cluster) distribution; presence and relative composition of cell populations; and, beyond these, cellular responses to the manufacturing process.

Accordingly, it is important, from the early stages of product development, to sufficiently explore CQAs (e.g., biological activity) at the cellular level of starting materials and cell banks, in order to ensure that the final drug product can achieve its intended safety, efficacy, and quality, and to develop appropriate analytical methods corresponding to those attributes.

It is generally recognized that release testing and in-process control testing alone are not sufficient to assess the impact of manufacturing changes. Therefore, additional characterization is recommended, using one or more analytical methods to assess each attribute. In particular, potency and/or biological activity should be evaluated using multiple analytical methods.

Manufacturing Scale

Comparability studies should be based on batches produced at the actual manufacturing scale of the investigational product. In principle, batches manufactured at a small scale or in a laboratory are not intended to be used as materials (target samples) for comparability studies; rather, they may provide useful supporting information for establishing comparability assessment strategies and study plans, whereby potential risks to product quality and process control are identified and the number of commercial-scale batches required for comparability assessment is determined. If production at the approved manufacturing scale is found to be

infeasible during the conduct of comparability studies, a risk assessment should be performed based on previously generated data for critical process parameters (CPPs), critical quality attributes (CQAs) such as biological activity and/or potency, and other relevant product attributes, in order to scientifically justify that the reduced manufacturing scale does not affect product quality and is appropriate for the assessment of product comparability.

Utilization of Batch Analysis Results

Test results from past batches can be compared with those of post-change batches; in such cases, analytical methods should be comparable across batches to ensure proper interpretation of the data. When analytical methods have changed as the development progresses, then retained samples from pre-change batches may be re-analyzed using the current methods. In cases where pre-change batches were manufactured using multiple processes or facilities, comparability should first be demonstrated across the pre-change batches prior to conducting comparability studies to assess the newly proposed change.

Number of Batches for Comparability Studies

Securing sufficient numbers of batches for comparability studies may be difficult, for example, when it is challenging to collect cellular starting materials from an adequate number of donors. It should be noted that an insufficient number of batches compromise statistical power and may be inadequate for meaningful comparison. In particular, where batch-to-batch variability is high, demonstration of comparability may become more difficult, and an appropriate comparability strategy should, therefore, be established.

Determining the Scope of Assessment and Additional Testing to Demonstrate Comparability for Manufacturing Changes

Comparability assessment should include relevant manufacturing steps to detect changes in CQAs. Where it cannot be clearly demonstrated that a process change does not affect the CQAs of the drug product, it is appropriate to collect, to the greatest extent possible, data spanning from the starting materials to the drug product to demonstrate comparability. When it is not feasible to establish a suitable *in vitro* potency assay, separate nonclinical or clinical studies may be required to support comparability at the nonclinical or clinical level. In such cases, the need for additional tests should be determined by comprehensively considering the following factors:

- Impact of manufacturing process changes on product purity, physicochemical, and biological characteristics
- Complexity of the active ingredient and impurity-related information, particularly for attributes susceptible to the manufacturing change
- Suitability of analytical methods for detecting expected product changes and the resulting data
- Association between CQAs and safety and efficacy based on previously generated nonclinical and clinical data

Recommendations for Comparability Assessment

For the assessment of product comparability, the following are recommended for developers to consider: (1) Characterization data on relevant physicochemical and biological quality attributes of the product; (2) Analytical results from appropriate samples collected at specific manufacturing steps (e.g., starting materials, intermediates, and drug products); (3) Detailed information on batches used to assess manufacturing consistency; (4) Accumulated batch data on observed variations in CQAs and on product safety and efficacy across single or multiple manufacturing process changes, including data confirming the absence of any unacceptable impact of such changes on safety and efficacy; (5) For cell-based products, consideration of the need to explore the appropriate range of manufacturing conditions, including stress conditions, in order to obtain information on the potential for product differences arising from alteration or denaturation of cells constituting the active substance (hereinafter "active cells") or of secreted factors (including, in particular, the differentiation and senescence status of the active cells, as well as potential differences in secreted factors and in cells present in the product other than the active ingredient); (6) Consideration of the need to explore and measure new sources of variability or new quality attribute indicators in order to understand the potential impact of manufacturing process changes on the quality, safety, and efficacy of the drug product; (7) Critical elements of process control that may affect product characteristics (e.g., downstream process(es) designated to process bulk material produced using the modified manufacturing process; and/or data describing the impact of the manufacturing change on product quality produced using the post-change downstream process(es)); (8) Justification of the process control, including critical control elements and in-process testing (e.g., an explanation of how such controls are maintained, partially modified, or newly established following the manufacturing change); and (9) Non-clinical characteristics of the final product and the intended therapeutic indication(s).

3. General Considerations for Manufacturing Changes

3.1. Considerations for Analytical Methods

Analytical methods used for comparability assessment of pre- and post-change comparability should be optimized to detect, to the greatest extent possible, changes in product quality attributes that may arise from the process change. In addition, where feasible, the application of multiple analytical methods based on different principles is expected to provide more reliable assessment results. This approach is particularly recommended when assessing: biomarker expression and/or secretion by target cells or by other non-target cell populations present in the product; the composition ratio between target cells and other cell populations in the drug product; residual levels of non-target cell populations with potential safety risks; and residual levels of non-cellular impurities.

To obtain data that are as easily interpretable as possible from comparability studies, it is necessary to analyze all pre- and post-change samples by conducting side-by-side testing using the same analytical methods and at the same facility. Where possible, reference materials should also be used. For example, when a new ELISA kit is introduced that may result in differences in sensitivity or precision, it is appropriate to assess the equivalence between the new and existing methods by testing both methods using the same samples.

Considerations for Selecting Analytical Methods

Using the pre-change analytical method as-is may make it difficult to detect product changes, due to limitations of the analytical methods (e.g., accuracy, specificity, and limits of detection) as well as the complexity of the drug product. Therefore, the following should be considered when selecting analytical methods for comparability assessment.

First, it should be determined whether the existing analytical methods are appropriate for their intended use or whether the methods need to be modified or changed. For example, if process changes result in changes to cell composition or to the characteristics (e.g., tumorigenicity) of potentially harmful non-target cell populations, it should be confirmed whether the analytical method used for their detection/quantification of non-target cell populations remains suitable for their intended purpose. In such cases, it may be appropriate to improve existing analytical methods to enable detection of newly emerging non-target cell populations.

Second, when existing analytical methods cannot adequately measure changes in quality attributes, new tests should be considered. In other words, new analytical methods should be developed when process changes (e.g., changes in manufacturing-related materials or culture processes) are reasonably expected to cause significant changes in quality attributes that cannot be detected by existing methods. In such cases, it is appropriate to use analytical methods offering improved performance compared with those previously used for characterization, routine release testing, or in-process controls.

Analytical methods used for comparability assessment should be scientifically sound and capable of generating reliable results. If characterization alone is not sufficient for comparability assessment, it is advisable to identify and assess new parameters in addition to existing CQAs. When the quality profile of the post-change product differs from that of batches used in non-clinical and clinical trials or other comparable batches, the significance of the difference should be assessed and presented with appropriate scientific justification. To enhance the reliability of comparability assessment following a manufacturing change, it is preferable to perform extensive and comprehensive characterization in advance, within the scope of attributes that can be appropriately evaluated, to the greatest extent feasible, using batches employed in pivotal clinical trials or batches manufactured using the same process, in order to fully understand the pre-change product and to accumulate a substantial amount of data, rather than relying on plans for additional characterization after the change. Such historical data may serve as useful supporting evidence for subsequent quality comparisons

and comparability assessments against the post-change product when future changes occur.

For comparability assessment of advanced biological products, the selection of analytical methods relevant to the functional and biological characteristics of the product is particularly important. Therefore, from the early stages of development, product characterization should be conducted in a multifaceted manner with future comparability assessments arising from manufacturing process changes in mind. The analytical methods used should be sufficiently specific, robust, and sensitive.

When selecting analytical methods for comparability assessment, it is recommended that the following factors be carefully considered.

1) Heterogeneity of Cell-Based Products

Given the inherent intercellular heterogeneity and non-uniformity of cell-based products, the presence and characteristics of non-target cells other than the active substance may affect the quality, safety, and efficacy of the product. Therefore, it should be confirmed that contaminating cells with potential safety concerns are present within acceptance limits. In addition, when differences are observed in the cytological or functional profiles of the active cells or contaminating cells in the drug product before and after a manufacturing process change, the potential impact of such differences should be assessed. If new types of cells are detected, their characteristics should be identified to the extent possible. Non-clinical or clinical studies may be required to confirm that the type and quantity of contaminating cells do not have an undesirable impact on the product’s safety or efficacy. Furthermore, reliance should not be placed solely on characterization of phenotypic purity markers; rather, the functional and biological characteristics of the product should be evaluated to comprehensively assess the impact of manufacturing changes on product quality, safety, and efficacy.

2) Potency Assay

As the biological activity and potency of cell and gene therapy products are highly sensitive to manufacturing changes, it is strongly recommended that a quantitative potency assay, as a key means of verifying these quality attributes, be included in comparability studies.

However, for advanced biological products, the mechanism of action is often not fully understood, and it is difficult to establish in vitro and in vivo assays that reliably predict

clinical efficacy. Furthermore, limitations of potency assays (e.g., high variability in assay readouts) may make it difficult to detect changes resulting from manufacturing process modifications. In addition, routine release testing alone may be insufficient or lack discriminatory capability to assess all aspects of a product's biological activity that may be affected by such changes. Therefore, consideration should be given to using multiple analytical methods to assess the biological activity and functional characteristics of the product as comprehensively as possible. Where available biological activity measurements and potency assays are considered insufficient to confirm that the efficacy of the product is maintained following a manufacturing change, additional non-clinical or clinical studies may be conducted. Animal models may be used to complement quantitative analytical methods in demonstrating biological activity and establishing comparability between pre- and post-change products. Although potency assays for advanced biological products are often established at a later stage of development and mechanism-based activity assays may be difficult to develop, it is nevertheless inadvisable to exclude potency testing from comparability studies.

When establishing acceptance criteria for potency in comparability studies, consideration should be given to the possibility that both decreases and increases in potency may negatively affect the product. Even intentional manufacturing changes that lead to a significant increase in potency may raise safety concerns. In such cases, unless it can be demonstrated that there is no negative impact on safety, the post-change product may not be considered comparable to the pre-change product.

3) Impurity Control

It is also necessary to assess changes in the profile of process-related impurities or adventitious agents. To ensure sufficient comparability assessment, analytical methods should be carefully selected and used in combination. When differences are identified in the profiles of process-related impurities or adventitious agents between pre- and post-change products, their potential impact on the safety and efficacy of the product should be reviewed. Furthermore, detected impurities should be characterized to the extent possible, and non-clinical or clinical studies may be required to confirm safety at the observed residual levels. In particular, contamination by infectious adventitious agents should be strictly controlled. If new contaminants are detected following a manufacturing process change, their impact on quality, safety, and efficacy should be assessed.

4) Specifications and Analytical Methods (Release Specifications)

Release specifications for drug products are generally established to confirm the quality of every batch produced in each manufacturing run rather than to analyze or interpret product characteristics. Accordingly, an assessment based solely on existing specifications and analytical methods is typically not considered sufficient to evaluate the impact of manufacturing process changes. Therefore, it is necessary to reconfirm whether the existing specifications and analytical methods remain appropriate for ensuring product quality following a process change. If results from post-change batches deviate from historical manufacturing data, this may indicate that a change in the product has occurred, in which case new analytical methods or acceptance criteria may be required. Where data or information indicate that specifications established prior to the process change are no longer suitable for routine batch analysis of the post-change product, consideration is recommended for modifying or deleting existing tests, or for adding new analytical methods. In general, changing specification limits or widening acceptance criteria is not considered appropriate unless adequately justified.

When the profiles of process-related impurities or non-target cells change following a process modification, and new impurities are detected in relatively large amounts, it is appropriate to establish specifications for such impurities.

Analytical methods used to demonstrate comparability within the release specifications for a drug product should be appropriately qualified or validated in accordance with the product's stage of development. Analytical methods used for characterization do not necessarily require validation; however, they should be scientifically valid, fit for their intended purpose, and sufficiently capable of detecting differences in product quality. In particular, as minor variations may have a significant impact on product quality, analytical methods should be sufficiently precise to provide reliable results. For example, where a 5% change in a specific cell surface antigen marker represents a difference in product, a flow cytometry method with a coefficient of variation (CV) of 20% would not be suitable for evaluating meaningful differences between pre- and post-change products.

In addition, test samples should be described in detail (e.g., in-process stage, sample volume, storage temperature), and any differences in sampling procedures between pre- and post-change processes explained.

5) Analytical Method Transfer

Analytical methods may be often modified, newly added, or transferred to new facilities. When analytical method transfer is conducted, the following should be taken into account:

- All analytical methods necessary to demonstrate product safety and efficacy should be included in the scope of the transfer.
- Analytical methods used in process validation studies for testing drug products, drug substances, raw materials, packaging materials, and residues should be transferred to the receiving units (RUs) prior to the conduct of process validation studies, and the RUs should be capable of appropriately performing these methods. Samples collected from process validation batches may be tested at the receiving units (RUs), sending units (SUs), or a qualified third-party laboratory after completion of the technology transfer.
- A step-by-step plan for analytical method transfer should be prepared. The analytical method transfer plan should include the objectives of the RUs and SUs, scope and responsibilities, details of reagents and analytical methods, study design and acceptance criteria, information accompanying test results and reporting formats (where applicable), deviation handling procedures, references, approval signatures, and details on reference materials (e.g., starting materials, intermediates, and finished products).

Refer to the following table for potential study designs and acceptance criteria for key analytical methods. For further details, reference may be made to "WHO Guidelines on Transfer of Technology in Pharmaceutical Manufacturing" (WHO Technical Report Series, No. 961, 2011, Annex 7). This table provides general guidance to support application of the principle that variability and sensitivity of analytical methods, as well as criteria for quality parameters should be considered during analytical method transfer. Alternative procedures and acceptance criteria may be applied based on scientific rationale and the characteristics of the analytical method and sample. When establishing study designs and acceptance criteria for key analytical methods, internationally accepted guidelines such as WHO Technical Report Series No. 961 Annex 7, ICH Q2(R2) “Validation of Analytical Procedures,” ICH Q14 “Analytical Procedure Development,” FDA Guidance on “Analytical Procedures and Methods Validation for Drugs and Biologics,” and USP <1224> “Transfer of Analytical Procedures” may also be consulted.

Table. Examples of Experimental Design and Acceptance Criteria for Analytical Testing [6]

Test	Considerations	Replicates	Set-up	Acceptance Criteria
Identity	• Focus on sample preparation, instruments, and data interpretation • Include in analytical method transfer plan, if relevant	• Single test is generally sufficient to demonstrate equivalence	-	-
Potency Assay	• Non-specific assays should not be used for stability testing • For multiple strengths, bracketing is possible	• Each site: 2 analysts x 3 batches (in triplicate) (= 18 per site)	• Different sets of instruments and columns • Independent solution preparation	• Comparison of mean and variability
Microbiological Testing (Qualitative and Quantitative Limit Tests)	• Implement common validation protocol: rationale, method identity, validation parameters, results summary, acceptance criteria, methods for data collection and analysis, handling of OOS results, follow-up requirements • Use same raw materials, technology, and inoculum preparation	• Validation in triplicate	• Use different batches for each validation exercise	• Qualitative: Demonstration of microbial recovery • Quantitative: Recovery within acceptance criteria specified in protocol
Impurities	• Confirm response factors relative to drug peak for calculation • Confirm LOQ at Receiving Unit (RU) • Compare chromatograms • Compare accuracy and precision for spiking tests	• Each site: 2 analysts x 3 batches (in duplicate) (= 12 per site)	• Different days, different sets of instruments and columns • Use of samples with similar age, homogeneity, packaging, and storage • Use spiked samples, if necessary	• (For low levels) RU values within ±25% of SU values, or RU mean within ±0.05% of SU mean

st. dev., standard deviation.

Note: Numbers in the table are given as examples only, and they should not be considered as recommendations.

The Receiving Units (RUs) and Sending Units (SUs) should implement the analytical method transfer plan and jointly prepare a report on the transfer results.

As with analytical method transfer, when the same analytical test is conducted at multiple facilities, an analytical method transfer study should be conducted to ensure reproducibility. To ensure consistency of results, the study should include test results

[6] For further details, refer to "WHO guidelines on transfer of technology in pharmaceutical manufacturing (WHO Technical Report Series, No. 961, 2011, Annex 7)". This table provides general guidance to support application of the principle that variability and sensitivity of analytical methods, as well as criteria for quality parameters during analytical method transfer. Alternative procedures and acceptance criteria may be applied based on scientific rationale and the characteristics of the analytical method and sample.

obtained using the same samples or common reference materials. Performing additional analytical method validation may help ensure the successful transfer of analytical methods to a new facility. General compliance requirements for analytical method validation are provided in Article 4 of the "Regulations on Good Manufacturing Practices for Medicinal Products" (MFDS Notification).

6) Stability of Drug Product

Product stability may be affected by changes in starting materials, or in culture conditions, washing, cryopreservation, physical processing (e.g., centrifugation), storage temperature, or cryopreservation media. Therefore, even minor manufacturing process changes may affect the stability of the drug product. In particular, where process changes alter product composition, such as residual impurities or formulation buffer, the impact on product stability should be evaluated. Therefore, it is recommended to initiate long-term stability studies for the post-change product when a change is implemented to the manufacturing process. Considering potential temperature deviations during transport or storage, stability testing under accelerated and stress conditions may be more informative than direct comparison of stability between pre- and post-change products during transport and long-term storage. In addition, establishing additional quality control parameters for manufacturing, transport, and storage may be considered to rule out unintended changes.

7) Establishment of Comparability Acceptance Criteria

To utilize a statistical approach for comparability assessment, equivalence acceptance criteria for quality attributes selected through a risk-based approach should be established in advance. Equivalence acceptance criteria for each CQA should be defined prior to initiating comparability studies. In addition to meeting equivalence criteria, batches used in comparability studies should meet established in-process control criteria and release criteria. Unless otherwise defined, the results should be representative of the data (e.g., mean, standard deviation, median) generated from historical pre-change batches.

If data obtained from other studies, such as impurity clearance or process characterization studies, provide evidence that a manufacturing change does not have a negative impact, such data may be used to justify the use of a reduced number of post-change batches for comparability assessment. Otherwise, comparability study should be performed using a sufficient number of post-change batches. If comparison is conducted

using a limited number of samples or batches, analytical results should be summarized together with descriptive statistics, and appropriate visual representations may be used to demonstrate that observed variations remain within the acceptance criteria.

For equivalence studies, the scope of historical data to be used, the statistical approaches, and the equivalence acceptance criteria should be appropriately selected and their justification described. In addition, consistency of product manufacture and the resulting equivalence in safety and efficacy should be ensured. Acceptance criteria may vary depending on the amount of available data and the selected statistical approach.

Equivalence acceptance criteria should not rely solely on statistical analysis of historical data: it must be grounded in an understanding of potential impacts on safety and efficacy. Clinical or manufacturing experience regarding CQA variations may be used to decide these criteria.

When statistical analysis of historical data is used to define acceptance criteria (e.g., based on standard deviation), the suitability of statistically derived acceptance criteria for ensuring the safety and efficacy of the post-change product should be appropriately justified. In other words, the relationship between the statistical acceptance criteria and biologically meaningful differences should be explained.

Where split manufacturing comparison (see Section 3.2) is not feasible, and it is known that variability in CQAs for the product and its clinical indication does not negatively affect product quality, safety, or efficacy, wider comparability acceptance criteria may be acceptable. In such cases, this approach may allow a reduction in the number of batches required for the equivalence assessment.

8) Statistical Approaches

Appropriate statistical methods should be employed when assessing the comparability of advanced biological products. As previously mentioned, statistical analysis methods should be included in the comparability assessment plan prior to the study.

For quantitative CQAs with normally distributed data, the equivalence margin can be defined as the maximum allowable difference from the population mean. When results fall outside this margin, this may be interpreted as the post-change process having a negative impact on product quality. Assessing equivalence by setting acceptance ranges involves verifying if post-change results fall within a defined range, which is typically narrower than the release specification for the same attribute.

Statistical approaches may be difficult when sample sizes are small, when quality attributes exhibit high variability, or when data do not follow a normal distribution. To prevent errors in comparability study design and analysis, it is important to carefully consider basic statistical concepts. In particular, certain statistical methods may be inappropriate due to incorrect hypothesis formulation, high variability in sample data, or limited information on the population. Therefore, the validity of the statistical analysis methods and the overall statistical approach, together with the associated hypotheses and predefined acceptance criteria should be justified, and limitations of the approach should be evaluated. Various statistical methods may be applied within a single study to analyze multiple CQAs. When the number of samples used for equivalence evaluation is small, sample variability tends to increase, resulting in reduced statistical power. Accordingly, an appropriate number of batches should be considered from the outset of the comparability study.

Statistical assessment of equivalence may also be difficult when analytical methods with low precision are used. In such cases, precision can be improved, and measurement uncertainty reduced, by performing multiple independent tests on the same batch and reporting the mean value. This approach can increase statistical power of the equivalence analysis for the attribute. However, note that the mean of these replicates must be treated as a single observation, rather than treating each replicate as an independent data point. In other words, there is one observation per batch.

When manufacturing is performed using split starting material from a single donor, paired data are generated for each donor. In such cases, appropriate statistical analyses should be selected to assess differences in paired data.

Furthermore, the absence of a statistically significant difference between pre- and post-change results (e.g., p-value > 0.05) does not demonstrate equivalence. For example, when the null hypothesis (H_0) is set to assume equivalence between pre-change and post-change conditions and the alternative hypothesis (H_1) to assume a difference the use of a two-sample t-test is not appropriate for claiming comparability. It should be clearly recognized that failure to reject the null hypothesis is not equivalent to demonstrating equivalence.

As previously noted, comparability is assessed by considering the confidence interval (CI) of the difference between pre- and post-change data; equivalence is established if the CI falls within the predefined equivalence margin. Where the relevant CQA result is expressed as a mean value, using the 'Two-One-Sided Tests procedure' (TOST) or other

appropriate methods may be considered. When application of TOST is not feasible, tolerance Intervals (99% or 95%) or a fixed standard deviation may be considered, depending on batch size. For other attributes (e.g., impurities, viability), general statistical comparisons, such as non-inferiority testing, may be used to demonstrate that the manufacturing change does not have a negative impact on product quality.

If the batches selected for equivalence evaluation are not representative of the routine manufacturing process, meaningful interpretation of the results may be difficult, regardless of the statistical method applied. Therefore, the selection of batches used for equivalence evaluation should be appropriately justified.

3.2. Considerations for Comparability Assessment Design

Although advanced biological products are outside the scope of ICH Q5E, the general principles outlined in this guideline may be applied. Comparability studies should be conducted in a stepwise manner, beginning with physicochemical and biological characterization, based on routine batch analyses, IPC, process validation, and characterization and stability data. In addition, comparability assessment should focus on those manufacturing process steps at which the impact of a process change is most likely to be detected. This may require assessment of raw materials and in-process controls in downstream steps following the process change. As previously noted, analytical methods should be suitable for the intended purpose and sufficiently sensitive to detect differences or changes in product characteristics. Any observed differences in analytical results should be assessed for their potential impact on product quality, safety, and efficacy.

A risk-based approach is recommended for changes. Changes expected to have a high impact require extensive comparability assessment across IPC, characterization, and release testing, and, where appropriate, additional or new analyses should also be considered.

For equivalence assessment, it is generally recommended to conduct parallel testing of pre- and post-change products within the same analytical run. To minimize both variation and deviation, side-by-side assessment—using products manufactured under identical conditions with the sole exception of the elements being changed—is preferred. In particular, cell-based products manufactured from different donors often exhibit a very wide range of product characteristics due to the inherent variability of the cellular starting material. As a result, the number of batches required to perform a statistically valid equivalence assessment may become excessively large, rendering statistical analysis

impractical. Therefore, to control variability arising from starting materials and to enable equivalence assessment with a limited number of batches, a comparative approach involving the manufacture and evaluation of products using split starting materials from a single donor is necessary. In particular, for autologous cell-based therapy products, the parallel manufacture and side-by-side analysis of products using split patient-derived starting materials is recommended to control patient-derived variability. Results obtained from this split approach should meet both IPC and release specifications and should be consistent with accumulated historical data. Where appropriate, paired difference analysis may be performed.

Where side-by-side, parallel analysis is not feasible, reliance on historical data may be unavoidable. In such cases, the potential impact of all variable parameters (analytical methods, personnel, equipment, or materials used) should be considered in the assessment. In particular, when parallel testing cannot be conducted (e.g., due to the unavailability of pre-change samples), emphasis should be placed on the analytical methods used for comparability assessment. Sufficient information on the analytical methods should be available to ensure the reliability of previously generated data. If different analytical methods are used for pre- and post-change products, establishing comparability (i.e., a meaningful relationship in term of quality, safety, and efficacy) between pre- and post-change products may be difficult. In such cases, conducting a bridging study between analytical methods should be considered.

Use of Surrogate Cellular Starting Materials

While it is recommended to use the same type of cellular starting material as that used for routine manufacturing for comparability assessments, a surrogate cell starting material (e.g., healthy donor cells instead of patient-derived cells) may be used when the availability of the original cellular starting material is limited or when the same type of cellular starting material cannot be obtained for other valid reasons. In such cases, the selection of the surrogate cellular starting materials should be justified. Consideration should be given to whether the use of a surrogate materials results in differences in process parameters and whether the surrogate starting material, when used as the cells for manufacture, allows for an effective assessment of product quality. For example, manufacturing using healthy donor cells may result in differences in transduction efficiency and therefore may not be an appropriate alternative. Additionally, for products intended to treat genetic diseases, healthy

donor cells lack the relevant genetic defect, rendering them potentially unsuitable for potency measurement.

Manufacturing Changes for Vectors Used in Transgene Introduction

For cell-based gene therapy products, changes to the manufacturing of vectors used for transgene introduction should be carefully assessed, not only for the risks to vector quality and the vector manufacturing process, but also for the potential risks to the quality and manufacturing process of the genetically modified cells. Comparability of the vector with respect to quality attributes should be assessed through release testing, including measurement of the biological activity of the vector, and through appropriate and relevant characterization. The impact of vector manufacturing changes on ex vivo gene therapy products (i.e., drug substance and/or drug product consisting of genetically modified cells) should be assessed using an appropriate number of batches of the vector as well as the drug substance and/or drug product. During product development, the number of vector batches available for comparability studies may be limited. In such cases, vector batches manufactured during process development may be included in the comparability assessment. However, the manufacturing process for these batches should be similar to that used for the vector employed in the investigational ex vivo gene therapy product. For changes related to cell-based gene therapy products, reference may be made to "Considerations for Development of Chimeric Antigen Receptor (CAR) T Cell Therapy Products" (Guidance for Industry).

3.3. Control of Post-Change Manufacturing Process

It is important to carefully assess the impact of manufacturing process changes on downstream processes and the quality attributes associated with each process (e.g., impact on reference values or acceptance criteria, in-process testing, critical process parameters, and other characterization attributes). When analysis of intermediates during manufacturing is used to predict potential changes in the drug product, the suitability of existing analytical methods to detect such changes should be evaluated. As previously mentioned, justification for this approach should be provided.

When in-process control parameters are re-established as a result of a manufacturing process change, it is necessary to confirm that intermediates manufactured under the newly established in-process control parameters are comparable to those produced using the pre-change manufacturing process. To demonstrate comparability, it is useful to show that specific intermediates are comparable and that residual process-related and product-related impurities are appropriately removed. As previously noted, the justification for the changes to the product is, in general, ultimately assessed based on data obtained from batches manufactured at commercial scale.

Manufacturing process assessment should be conducted by comprehensively considering factors such as the criticality of the process, the step at which the change is implemented and its impact on other processes, as well as the nature and extent of the change. Process assessment may draw upon data, including information generated during process development and data derived from small-scale model qualification studies; prior experience with process changes; experience with similar equipment or operations; information on similar changes in comparable products; and relevant literature.

When manufacturing process changes are implemented, including the introduction of new in-process control parameters, it is necessary to demonstrate that the post-change process is capable of producing products of comparable quality, taking into account the interrelationship among in-process controls.

Control for the post-change manufacturing process should include, as appropriate, the following:

- Establishment of post-change specifications and analytical methods for starting materials (e.g., source cells for manufacture), other raw materials, supplies, and ancillary materials
- Viral safety evaluation of the post-change cell bank when changes are made to the cell bank serving as the cells for manufacture
- Testing and control of adventitious infectious agents
- Control of product-related and process-related impurities (e.g., impurity reduction rates)

4. Considerations for Nonclinical and Clinical Studies

If comparability cannot be ensured solely through analysis of quality attributes of pre- and post-change products, additional nonclinical or clinical studies may be conducted to support the demonstration of comparability. In particular, nonclinical studies may be required to support quality changes to the investigational medicinal product after clinical trials are initiated. Where analysis of quality attributes alone is insufficient to determine the potential impact on the drug product, nonclinical studies can contribute to the demonstration of comparability. The scope and design of nonclinical and clinical studies for comparability assessment are determined on a case-by-case basis, taking into account various relevant factors, including the specific quality attributes showing differences in the post-change drug product and the magnitude of those differences. Test results related to the physicochemical and biological characteristics of the product should be referenced. Additionally, quality differences between materials used in nonclinical studies and investigational medicinal product batches should be considered. For example, where new impurities are present, justification regarding their residual levels or permissible limits should be provided, and toxicity studies may be required.

Nonclinical or clinical studies for comparability assessment may include pharmacokinetic (PK) studies, biodistribution studies, nonclinical efficacy studies, various safety studies, immunogenicity studies, and clinical trials (including post-marketing clinical trials on safety and efficacy).

As noted above, if comparability cannot be established through quality assessment or nonclinical studies, the safety and efficacy evidence accumulated from clinical studies using a pre-change product may not be sufficient to support the demonstration of comparability of the post-change product.

If the potential impact of a manufacturing process change on safety cannot be determined by quality and nonclinical comparability assessments alone, it may be necessary to conduct new clinical trials and/or implement additional safety measures in ongoing trials (e.g., expanding the scope of the adverse event monitoring, sequential enrollment of subjects, revising stopping rules). Where a manufacturing process change is not expected to negatively affect product safety but a negative impact on product efficacy cannot be excluded, the efficacy of the post-change product should be evaluated in clinical trials. In addition, clinical data from subjects treated with the post-change product are intended to be

pooled with clinical data obtained using the pre-change product, comparability between the pre- and post-change products should be demonstrated, and the clinical trial design should be shown to support such pooling.

If quality analyses and/or nonclinical comparative studies fail to demonstrate that a manufacturing process change does not adversely affect product quality, the approval of the proposed change to the manufacturing process is not possible, and the conduct of new clinical trials to re-evaluate the safety and efficacy of the post-change product may be considered.

5. Data Requirements for Amendment to Clinical Trial Applications

To facilitate the approval process for amendments to clinical trial applications resulting from manufacturing process changes to investigational medicinal products, developers should prepare and submit data in accordance with the requirements below. The type, content, and scope of documentation to be submitted may vary depending on the product, the stage of clinical development, and the extent of the proposed change.

Detailed requirements for the comparability assessment report are as follows:

(1) Overview of Comparability Assessment

- Purpose of the change
- Comparability assessment strategy
- Explanatory materials detailing the changes and a change comparison table
- Information on relevant batches
- Summary of clinical experience to date
- Clinical development stage and the number of subjects to receive pre- and post-change products

(2) Analytical Methods for Comparability Assessment

- Tabulation of analytical methods and testing laboratories used for comparability assessment (recommended)
- Explanation of analytical methods for Critical Quality Attributes (CQAs) that are still under development, if applicable

(3) Rationale for Comparability Assessment Design

- For risk-based approaches: description of risk assessment methodology, assignment of risk levels to comparability attributes, and detailed justification
- Explanation of statistical analysis methods used

(4) Comparability Assessment Results

- A comparative table summarizing results for each quality attribute and process parameter evaluated for pre- and post-change batches
  - ★ Summarized statistical analysis results with predefined equivalence acceptance criteria; graphical presentations (e.g., plots) are recommended
- Explanation and analysis of observed differences between pre- and post-change products
  - ★ Determination of comparability based on evaluation of the totality of comparability data, including all historical manufacturing data
  - ★ A detailed description and scientific justification of any deviations from predefined procedures or acceptance criteria

(5) Discussion of Comparability Assessment Results

- Summary of comparability test results and discussion based on data analysis
  - ★ Potential limitations of the comparability study
  - ★ Justification and additional scientific evidence supporting the conclusion of comparability where quality attributes do not meet predefined acceptance criteria but the pre- and post-change products are nevertheless considered comparable
- Appropriate revision of relevant sections of the Investigational Medicinal Product Dossier (IMPD) to reflect the change
  - ★ Comparability data should be presented, together with manufacturing and quality changes, as part of the detailed description of the manufacturing process development history within sections 3.2.S.2.6 or 3.2.P.2.3 (Manufacturing Process Development) of the IMPD. For each change, the comparability assessment plan and results should be provided, including batches used, analytical methods, and statistical methods applied. Development history data should be cumulatively updated to incorporate changes implemented throughout development process.
  - ★ When applying for quality-related amendments to a Clinical Trial Application in accordance with the "Guideline on Quality of Investigational Medicinal Products," submit a quality change comparison table and a statement confirming the absence of additional quality changes.

(6) Submission Data for Prior Changes

- Summary of previous manufacturing changes and their impact on process consistency and product quality.
- Information on previous changes to product specifications, including those for drug substance, drug product, and key intermediates

6. Other Considerations

Manufacturing and Quality Changes Requiring New Clinical Trial Application

Examples of manufacturing and quality changes for which submission of a new clinical trial application may be appropriate include: changes to starting materials for cell-based therapy products (e.g., allogeneic vs. autologous; adipose-derived vs. umbilical cord-derived); changes to the types of cells constituting the active substance (e.g., CD4+/CD8+ mixture vs. CD4+); changes to the capsid or envelope of viral vectors that may alter vector tropism or serotype; modifications to transgene sequence(s) or addition of transgene(s) (e.g., the intracellular signaling domain of a CAR construct); changes to expression regulatory elements within viral vectors (e.g., tissue-specific vs. ubiquitous transcription factor); and changes to gene-editing targets, including addition of target gene(s), for gene editing products.

When Analytical Methods Used Cannot Sufficiently Detect Changes with the Potential to Affect Product Safety and Efficacy

When pre- and post-change products appear highly similar, but analytical methods used cannot sufficiently detect changes that may affect product safety and efficacy, additional characterization, and/or nonclinical or clinical studies should be considered to reach a clear conclusion. This situation may arise particularly when differentiation induction methods or culture methods for cell-based therapies are changed. Changes to differentiation induction methods or culture methods are highly likely to alter the biological characteristics of the final cells constituting the active substance. Accordingly, if comparability of attributes relevant to safety and efficacy cannot be sufficiently confirmed through additional characterization, the likelihood that additional nonclinical or clinical studies will be required increases. In such cases, it may be reasonable to use existing non-clinical or clinical results as reference data and pursue product development through a new clinical trial. Also, for product classes with limited accumulated clinical data (e.g., induced pluripotent stem cell (iPSC)-based therapy products), changes to the cell bank used as a starting material may make it difficult to sufficiently demonstrate comparability of safety and efficacy, even when all quality attributes measurable using current technologies are evaluated; therefore, planning a new clinical trial may be appropriate.

Minimum Number of Batches for Comparability Assessment

It is not possible to universally specify a minimum number of batches for comparability assessment. To confirm comparability at the required level, the number of batches should be determined and tested taking into account the product's inherent variability. Depending on the type of change introduced, a strategy employing a limited number of batches together with analytical methods of high precision and sensitivity methods may be feasible. However, for biological characterization, more extensive testing using a sufficiently large number of batches due to the high inherent variability of biological attributes. The number of batches to be included in the comparability assessment should be determined on a case-by-case basis, considering factors such as product characteristics and the significance of changes. The selected comparability assessment strategy should be justified based on careful consideration of the type of change, the level of understanding of the product and manufacturing process, the overall process control strategy, the suitability of analytical methods, and the level of risks associated with the change.

Comparability Assessment for Addition of or Change to a Manufacturing Facility

When a manufacturing facility is added to, or an existing manufacturing facility is changed from the current facility, the comparability of products manufactured at the added or changed facility should be assessed comprehensively and extensively. The first step is to demonstrate the suitability of process transfer by assessing equivalence of the process and analytical procedures through equivalence assessment of the process itself, including evaluation of process parameters and IPCs, thereby establishing the appropriateness of the manufacturing process prior to transfer. The second step is to assess comparability of the product itself through sufficient characterization and release testing. In this assessment, the suitability of each analytical method used to evaluate comparability should be considered. For equivalence acceptance criteria and statistical analysis methods, refer to the principles described in the previous sections.

Use of Healthy Donor-Derived Starting Materials

For cell-based therapy products, assessment of comparability using patient-derived starting materials may be impracticable due to practical constraints. Healthy donor materials may be used where patient-derived materials are limited or where ethical considerations preclude their use. In such cases, the representativeness of healthy donor–derived starting

materials should be justified, for example, by demonstrating that patient cells exhibit gene transduction efficiency comparable to that observed in healthy donor cells. In addition, the representativeness of the manufacturing scale employed should be verified.

7. References

(1) Regulation on Approval of Investigational New Drug (IND) Plans (MFDS Notice No. 2024-2, Jan. 16, 1. 2024)

(2) Guideline on Comparability Assessment for Changes in Manufacturing Methods of Biological Products (NIFDS, 2023)

(3) Guideline on Quality Assessment of Investigational Cell and Gene Therapy Products (NIFDS, 2022)

(4) Guideline on Quality Assessment of Gene Therapy Products (NIFDS, 2022)

(5) Guideline on Quality, Non-clinical, and Clinical Assessment of Stem Cell Therapy Products (NIFDS, 2024)

(6) Guideline on Good Manufacturing Practice (GMP) for Advanced Biological Products (MFDS, 2020)

(7) Commentary on Good Manufacturing Practice (GMP) for Biological Products, etc. (MFDS, 2019)

(8) ICH Q1A(R2) Stability Testing of New Drug Substances and Products (ICH, 2003)

(9) ICH Q2(R2) Validation of Analytical Procedures (ICH, 2023)

(10) ICH Q5A(R2) Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin (ICH, 2023)

(11) ICH Q5C Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products (ICH, 1995)

(12) ICH Q5D Derivation and Characterization of Cell Substrates Used for Production of Biotechnological/Biological Products (ICH, 1997)

(13) ICH Q5E Comparability of Biotechnological/Biological Products Subject to Changes in their Manufacturing Process (ICH, 2004)

(14) ICH Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products (ICH, 1999)

(15) Considerations for the Use of Human- and Animal-Derived Materials in the Manufacture of Cellular and Gene Therapy and Tissue-Engineered Medical Products, Draft Guidance for Industry (FDA, 2024)

(16) Manufacturing Changes and Comparability for Human Cellular and Gene Therapy Products, Draft Guidance for Industry (FDA, 2023)

(17) Guideline on Quality, Non-Clinical and Clinical Requirements for Investigational Advanced Therapy Medicinal Products in Clinical Trials (EMA, 2025)

(18) Questions and Answers: Comparability Considerations for Advanced Therapy Medicinal Products (ATMP) (EMA, 2019)

(19) Guideline on the Requirements for Quality Documentation Concerning Biological Investigational Medicinal Products in Clinical Trials (EMA, 2018)

(20) 「ヒト細胞加工製品の製造工程の変更に伴う同等性/同質性評価に関する指針」及び質疑応答集【Q&A】について (PMDA, 2024)

(21) WHO Guidelines on Transfer of Technology in Pharmaceutical Manufacturing in: Transfer of Technology in Pharmaceutical Manufacturing (WHO Geneva, World Health Organization (WHO Technical Report Series, No. 961, 2011), Annex 7)

Guideline on Comparability Assessment of Investigational Cell and Gene Therapy Products (Guidance for Applicants)

Date of Issue	May 2026
Publisher	Seogyoun Kang
Editor-in-Chief	Youngju Choi
Editorial Committee	(Cell and Gene Therapy Product Division, Biopharmaceuticals and Herbal Medicine Evaluation Department) So-young Wang, Jounghee Baek, Jin Wook Kang, Su Kyoung Seong, Young Ki Hong, Donghyun Park, Gayoung Lee, Hyesun Yu, Jaerin Lee, Nahee Park, Myeong Sook Moon, Hye-Ryeon Heo, Jin Shil Choi, Hee Young Park, Soojeong Cheon, Jiyeung Lee
Contributors	*MFDS Early Bird Research Group* *Dynamic Bio Advanced Biological Products Division Working Committee:* Mi-hyun Jung (Chair, Advanced Biological Products Div. Working Committee/CTX), Kyung-hwan Noh (Subcommittee Chair, Cell Therapy Products/Artblood), Hyun-jin Seo (Subcommittee Chair, Gene Therapy Products/Curocell), In-ja Lee (Secretary, Advanced Biological Products Div./Medipost), Ji-hye Kwak (Organoid Sciences), Hye-seon Kim (Cellatoz Therapeutics), Kwang-moon Baek (ENCell), Ji-hye Seok (Medipost), Isaac (GC Cell), Sun-rye Lee (CEFO Bio), Yeon-kyung Lee (CellinCells), Young-ha Lee (AbClon), So-yoon Lim (Eutilex), Mi-seon Choi (Kangstem Biotech), Young-ji Choi (Thermo Fisher Scientific Korea)
Published By	Cell and Gene Therapy Product Division, Biopharmaceuticals and Herbal Medicine Evaluation Department, National Institute of Food and Drug Safety Evaluation (NIFDS)
Tel	+82-43-719-3538
Fax	+82-43-719-3530