Provisional Translation (as of March 2025)*

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To：Directors of Prefectural Health Departments (Bureaus)

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

# Projects for preparing evaluation guidance for next-generation medical devices and cellular- and tissue-based products

The Ministry of Health, Labour and Welfare has been studying evaluation indices for next-generation medical devices and regenerative medical products, which have high medical needs and are likely to be used practically, with the aim of increasing the efficiency of product development and accelerating approval reviews by preparing and publishing the technical evaluation indices used in the review.

Recently, we have compiled evaluation indices for the conditions and time-limited approval of human cell processing products made from human-derived mesenchymal stem cells or mesenchymal stromal cells, as well as the points for the subsequent efficacy evaluation plan. Please notify the related organizations under your jurisdiction of this Notification to utilize as a reference for the marketing authorization application.

Please note that a copy of this notification will be sent to the relevant organizations and the Pharmaceuticals and Medical Devices Agency (PMDA) as stated in the separate document.

Remarks

1. Evaluation guidance indicates items (endpoints) that should be focused on in the evaluation of a product from the viewpoint of gathering application dossiers and expediting their review. It should be kept in mind that evaluation guidance are not positioned as legal standards, but rather indicate evaluation items that are currently considered for next-generation medical devices and regenerative medical products with remarkable technological developments. In accordance with the characteristics of the products, evaluation items other than those shown in the evaluation indices may be required or there may be items that do not need to be applied among the evaluation items shown in the evaluation indices.
2. When collecting the data and data required for the application for approval of individual products, it is desirable to utilize the consultation with PMDA as early as possible, in addition to considering the items indicated in the evaluation indices in advance.

# Guidance on Conditional and Time-Limited Approval for Human Cell-Processed Products Derived from Mesenchymal Stem Cells or Mesenchymal Stromal Cells of Human Origin and Evaluation for Subsequent Efficacy Evaluation Plan

## 1. Introduction

Among regenerative medical products (as defined in Article 2, paragraph (9) of the "Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices"(PMD act) (Act No. 145 of 1960), the fundamental technical requirements for ensuring the quality and safety of human (autologous) somatic stem cell processed products and human (allogeneic) somatic stem cell processed products are stipulated in the " Guidelines on ensuring quality and safety of products derived from processed cell and tissue (Autologous somatic stem cells)" (Notification No. 0907-2 by the Director of the Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare, dated September 7, 2012; hereinafter "Guidelines for Human (Autologous) somatic stem cell processed products") and the " Guidelines on ensuring quality and safety of products derived from processed cell and tissue (Allogeneic somatic stem cells)" (Notification No. 0907-3 by the Director of the Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare, dated September 7, 2012; hereinafter "Guidelines for Human (Allogeneic) somatic stem cell processed products"). This document outlines considerations for human cell processing products that use mesenchymal stem cells or mesenchymal stromal cells (collectively referred to as MSCs) derived from humans (referred to as "human MSC processing products"). It provides guidance on additional points to consider beyond the fundamental technical requirements for conditional and time-limited approval (as defined in Article 23-26 of PMD act). It also specifies considerations for developing efficacy evaluation plans as approval conditions for such conditional and time-limited approvals.

## 2. Subject–

This document sets out the points to be noted when considering the applicability of conditional and time-limited approvals for human MSC processed products, and the points to be noted when formulating an efficacy evaluation plan as conditional and time-limited approvals, to regulatory reviewers and applicants for marketing approvals for human MSC processed products. The information provided in this document may also be relevant to regenerative medical products other than human MSC processed products. However, it is recommended that marketing authorization holders consult with the Pharmaceuticals and Medical Devices Agency (PMDA) as to how to refer to the content of this document.

## 3. Scope

This document presents the points that should be considered at present, taking into account the characteristics common to human MSC processed products and the characteristics common to regenerative medicine (regenerative medicine prescribed in Article 2 of the PMD act (Act No. 85 of 2013)) using human MSC processed products. It is not necessarily intended to be exhaustive.

Therefore, these are revised based on further technological innovation and accumulation of knowledge in the future, and are not binding on the content of applications, etc.

In determining the conditions and time-limited approvals for human MSC processed products, and in examining the subsequent efficacy evaluation plan, it is necessary to respond flexibly so that the required information can be collected, while aiming at minimizing "the possibility that reasonable judgment or the evaluation cannot be achieved" with full understanding of the characteristics specific to individual products. It is recommended to consult with PMDA regarding the evaluation required for individual products. In addition to this document, other relevant guidelines of both domestic and international should also be referred.

## 4. Defined Terms

The terms used in this document are defined in 1) to 3), in addition to the definitions of "Guidelines for Human (Autologous) somatic stem cell processed products" and "Guidelines for Human (Allogeneic) somatic stem cell processed products"

1) Mesenchymal stem cells

   A type of somatic stem cell derived from mesodermal tissue (mesenchyme) that meets the following three criteria: i) adheres to a plastic culture vessel, ii) is positive for CD105, CD73, CD90 and negative for CD45, CD34, CD14, CD11b, CD79a, CD19, HLA-Class II (DR), and iii) is capable of differentiating into mesenchymal cells (bone, fat, and cartilage). They can be isolated from adipose tissue, bone marrow, umbilical cord, pulp, etc. Moreover, they have the immunomodulatory function by the action of not expressing MHC Class-II and secreting cytokine and growth factor, etc., and features such as promoting tissue regeneration and repair are shown.

2) Mesenchymal stromal cells

   Fibroblast-like cells derived from mesodermal tissue (mesenchyme) and adhered to plastic culture vessels. Mesenchymal stromal cells that meet certain criteria are called mesenchymal stem cells.

3) MSC

   Mesenchymal stem cells or mesenchymal stromal cells.

## 5. Points to Consider in the Review of Marketing Approval for Processed Human MSC Processed Products

Article 11 of the Act Regarding Policy Package to Provide National Citizens Regenerative Medicine Timely and Safely (Regenerative Medicine Promotion Act) (Law No. 13, 2013), which was enacted in 2013, states that "Taking into account the characteristics of regenerative medical products, in order to seek early approval in accordance with the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices and ensure the safety of regenerative medical products, the government shall take the necessary measures to secure the human resources for reviewing regenerative medical products, to improve transparency of the review of regenerative medical products, and to develop systems for reviewing regenerative medical products."

Article 2-2 of the Regenerative Medicine Promotion Act states that "Taking into account the characteristics of regenerative medicine, comprehensive efforts with organic coordination and effectiveness should be promoted in order to promote quick and safe research and development and provision, and dissemination, while giving consideration to bioethics." Therefore, when considering conditional and time-limited approvals in the review of marketing approvals for human MSC processed products, the characteristics of human MSC processed products themselves and the characteristics of regenerative medicine using human MSC processed products should be taken into consideration.

### 5.1. Properties of human MSC processed products

#### 5.1.1. Heterogeneity of human MSC

Among human MSC, human mesenchymal stem cells can differentiate into mesenchymal cells, such as bone, fat, and cartilage. However, there are not many cases of the development of human cell-processing products that are mainly composed of specific mesenchymal cells which obtained from human MSCs and differentiated *in vitro*. Rather, many processed human MSC products are mainly composed of human MSC processed such as culture (hereinafter "processed human MSC").

Among human MSC, human mesenchymal stromal cells simply refer to fibroblast-like cells derived from mesodermal tissue (mesenchyme) and adhered to plastic culture vessels, and there are no known biomarkers such as cell surface antigens specific for human mesenchymal stem cells. In other words, human mesenchymal stromal cells or human mesenchymal stem cells are generally composed of a subpopulation of cells rather than a homogeneous population of cells.

Therefore, although processed human MSC, can be said to be “homogeneous” between manufacturing batches only in that it is a population of cells that satisfies the quality specifications and characterization criteria that are considered to be necessary for ensuring a certain level of efficacy and safety, unlike conventional small molecule drugs and biopharmaceuticals. Even if all measurable quality attributes in current technology are listed, not all of the critical quality attributes and quality variables required to fully assure efficacy and safety can be completely identified or covered. In other words, the processed human MSC is likely to be heterogeneous consisting of a plurality of cellular subpopulations that differ in properties not captured by a given quality specification or characterization. It is essential to recognize that efforts are needed to understand the heterogeneity of this subpopulation of cells in order to ensure the continuous reproducibility of the efficacy and safety of the processed human MSC.

#### 5.1.2. Divergent mechanisms of action of human MSC

In general, to ensure the continuous reproducibility of the efficacy of drugs, etc., it is important to understand the mechanism of action and to understand and control the quality attributes related to the mechanism of action. Various physiological effects are known in human MSC, including immunosuppressive (anti-inflammatory) effects, tissue regenerative effects, angiogenic effects, antifibrotic effects, antioxidative stress effects, anti-apoptotic effects, and migration ability to pathological sites (ischemic and inflammatory sites). Therefore, it is generally difficult to quantitatively understand at the non-

clinical stage how the various physiological functions of the processed human MSC exert their effectiveness while interacting in the patient. Although it may be possible to estimate the mechanism of action in preclinical proof-of-concept studies (efficacy or performance support studies), in order to correctly understand the mechanism of action of processed human MSC in the clinical setting, the analysis by comparing the product-quality data with the clinical data is more important than in the case of conventional drugs or biopharmaceuticals. Also, even among a plurality of human MSC products if the main mechanism of action for the indication differs, the critical quality attributes closely related to the effectiveness of each product may differ from product to product.

#### 5.1.3. Differences between donors in the qualities of autologous human MSC processed products

MSC may be obtained from the donor of the subject patient (autologous human MSC) or from a donor that is not the subject patient (allogeneic human MSC). Advantages of autologous human MSC products include that it does not require as strict control as allogeneic human MSC products regarding contamination with infectious agents such as viruses. However, since autologous MSC processed products have the following characteristics and there is a high possibility that heterogeneity of quality will occur due to differences in starting material cell donors (patients), careful quality development planning based on these characteristics is required.

1) When it is difficult to obtain samples derived from patients before the start of the clinical trial and when characterization is performed using samples derived from healthy individuals, the results of characterization of the test product obtained at the start of the clinical trial and the results of characterization of the clinical trial product performed using cells derived from patients may not necessarily be the same.
2) For autologous processed MSC products that need to be manufactured on a patient-by-patient basis, the validity of the quality control strategy for the clinical trial product and the preparation of a verification master plan based on the strategy are required. Therefore, quality consultation with PMDA after the start of the clinical trial should be utilized and development of the quality control strategy should be proceeded with caution. For autologous MSC products, cell characteristics other than those specified in the quality specification vary from patient to patient, and process variables are complex and difficult to identify.
3) There is a limitation in the amount of product that can be manufactured, and it is considered that sufficient sample volume cannot be obtained in performing the characterization.

### 5.2. Characteristics of regenerative medicine using human cell processed products

#### 5.2.1. Severity of target diseases, etc.

Human cell processing products as new medical modalities are expected as a means of providing new therapies for diseases that are difficult to treat with conventional technology. Especially in the case of Japan, where it is difficult to secure human organs, tissues, or human cells, it is expected to be a great alternative to transplantation therapy. Voices of hope for its practical application and spread are reflected in

Regenerative Medicine Promotion Act.

In particular, it is essential to ensure that the products used to treat patients who suffer from diseases that cannot be cured by conventional therapies due to limitations, such as 1) severity and life-threatening diseases, 2) diseases that seriously impair the function of the body, or 3) diseases that significantly impair QOL(quality of life) by impairing the function or form of the body to a certain extent, are accessible to the patients as soon as possible while ensuring safety. Therefore, designated human cell processed products for orphan regenerative medical products, SAKIGAKE/pioneering regenerative medical products or special purpose regenerative medical products are expected to receive marketing approval as soon as possible.

#### 5.2.2. Regenerative medical products used in conjunction with surgery

Regenerative medical products that use human cell processed products are broadly divided into two types: treatments that do not require surgery, such as intravenous administration of the product, and treatments that require surgery when the product is administered. In the treatment which needs the surgery, trial and error until the technique establishment are necessary in some cases. For this reason, especially in regenerative medical products that require surgery, it is necessary to fully investigate the surgical method and to appropriately inform healthcare providers of the surgical method and precautions based on the results of clinical trials, which is different from the conventional treatment using many small molecule drugs and biopharmaceuticals. In addition, post-marketing information on surgical procedures should be collected and reviewed, and any new findings should be appropriately provided to healthcare professionals.

### 5.3. Consideration for Conditions and Time-Limited Approval of Human MSC Processed Products

According to Article 23-26 of PMD act, the Minister of Health, Labour and Welfare may grant marketing approval (conditional and time-limited approval) for regenerative medical products that fall under any of the following categories with the conditions necessary for ensuring proper use and a time limit not exceeding 7 years.

1) the regenerative medical products pertaining to the application have heterogeneity
2) the product is deemed to have efficacy, effects or performance pertaining to the application
3) the item pertaining to an application is deemed as not being of value as a regenerative medical product pertaining to an application due to its significantly harmful action for its efficacy or performance

Concerning the requirements of Article 23-26, paragraph (1), item (i) for processed human MSC, Section 5.1 of this document should be considered. That is, by the time of the marketing approval review, which is conducted again after the conditional and time-limited approval, it is necessary to clarify what is planned to be elucidated for 1) understanding of the heterogeneity of the human cell population that is the main component of the human MSC processed product, 2) understanding of the main mechanism of action and important quality attributes related to clinical efficacy, and 3) understanding of the variation in quality of the final product due to differences in the source cell donors. Even if it is inevitable that the quality is not homogeneous at the beginning of the product life cycle, it is necessary to understand and manage the

heterogeneity of the quality to the extent possible in order to ensure the continuous reproducibility of the efficacy and safety of the product.

The level of evidence for the efficacy required for "the product is deemed to have efficacy, effects or performance pertaining to the application" in Article 23-26, paragraph (1), item (ii) shall be determined for each product, while taking into consideration the characteristics of the product described in Section 5.2. Next, the level of evidence of efficacy is determined by identifying the risk that remains after reducing the clearly assumed risk of administering the product (including the risk of lost opportunities for other therapies) to the extent technically feasible and scientifically reasonable, and by considering the balance between this and the presumed benefit.

## 6. Considerations to be noted in the evaluation based on the approval condition evaluation plan after the conditional and time-limited approval

For the conditional and time-limited approval of regenerative medicine products such as human MSC processed products, it is important to estimate the ultimate benefit of the product to the patient during the life cycle of a series of clinical developments, and then to examine information on a certain degree of efficacy obtained from exploratory clinical trials at an early stage of development, as well as information on efficacy (and safety) obtained from evaluations conducted based on the conditions of approval after marketing. In other words, it is appropriate to consider the launch of the product under the conditional and time-limited approval as developing phase of the life cycle of clinical development followed by a subsequent routine approval review and reexamination.

Therefore, for clinical development that undergoes conditional and time-limited approval, a rational and feasible plan for the evaluation of efficacy and safety in the evaluation of post-marketing approval conditions should be presented before the conditional and time-limited approval.

Points to consider in the post-marketing assessment include (1) the number of patients, (2) the number of study sites, (3) objectivity of the endpoints, (4) randomization of patients, (5) blinding of the assessment, and (6) setting of control group and method of data collection (prospective or retrospective). If above of these are judged to be not appropriate, obtained data will not the basis for full approval. When considering the applicability of conditional and time-limited approval, the applicant and the regulatory authority need to explain the validity of (7) methods for collecting post-marketing information based on (1) to (6). This is because regenerative medical products are not necessarily homogeneous in ingredients, and based on the heterogeneity of ingredients, it is assumed that in many cases it is difficult to obtain a sufficient number of patients and facilities at the clinical trial stage in order to conduct efficacy evaluation. It is also difficult to blind due to the fact that they are targeted for rare or severe diseases or require surgery, making it difficult to evaluate them within the framework of a normal clinical trial. As it is important to plan the post-marketing approval condition assessment for the product with conditional and time-limited approval, applicants and regulatory authorities should clarify the validity of the plan, including (1) to (7) above, and clarify the achievement criteria in advance. If the product does not meet the achievement criteria agreed between the applicant and the regulatory authority in the post-marketing approval condition assessment, the product may

not be approved because its efficacy of the product cannot be confirmed.

If it is not possible to prospectively obtain a comparative control group, such as a natural history, as part of the evaluation of post-marketing conditions, then the method of efficacy evaluation that can be chosen will be limited, and the available endpoints will be limited. If the study design is not appropriate to explain clinical efficacy, it will be difficult to proceed toward full approval because the benefits of the product to patients will not be explained.

The considerations for each of (1) to (7) are described below.

**(1) Sample size**

In principle, the minimum sample size for the efficacy evaluation in the post-marketing approval condition assessment should be set so that clinically meaningful endpoints can be statistically assessed. However, the sample size may vary depending on the number of patients in Japan, the severity of the target diseases, QOL of patients, and the presence or absence of alternative treatments. Therefore, the minimum sample size should be agreed between the applicant and the regulatory authority for each product, taking these factors into account. It should be noted that the sample size of the control group is important in cases where it is difficult to verify efficacy based on the properties of MSC as described in the section 5.1. If a sample size redesign based on interim analysis is planned, it is necessary to clearly define the procedure in advance.

**(2) Number of evaluation sites**

In principle, it is desirable that the number of evaluation sites in the post-marketing approval condition assessment is multiple so that differences between sites can be examined. On the other hand, from the viewpoint of the impact of product storage and transport on product quality, the number of evaluation sites may be limited due to the limitation of the location of the post-marketing approval assessment site and the location of the manufacturing site. In such cases, the applicant should explain the appropriateness of conducting the evaluation at a small number of sites.

**(3) Objectivity of endpoints**

It is recommended that the endpoints will be those which do not appear to be biased toward evaluation, such as patients, evaluators' subjectivity, or differences between sites. Particularly in the open-label study, endpoints should be set that have little or no impact on the evaluation if patients or study personnel are aware of the treatment group (e.g., mortality). As far as possible, objective and quantitative endpoints should be used. If endpoints are subjective, the data from the post-marketing approval condition assessment are unlikely to be robust due to the effects of bias. Therefore, if objective and quantitative endpoints are not used, the applicant should explain the necessity or justification. For efficacy endpoints, the success criteria should be established in advance before the post-marketing approval condition assessment. In addition to considering the fact that many products are difficult to randomize or blind in the post-marketing approval condition assessment, the evaluation items and their success criteria should be established taking into account such factors as natural healing. Assessment methods should be standardized between evaluators

and between study sites.

**(4) Randomization of cases**

Randomization of cases in use-results surveys, etc. may be difficult. In particular, when the conventional treatment is not effective in the indication of a conditional and time-limited product, the product is preferentially used in the target patient, and it may be difficult to set a group（control group) in which the product is not used, making it difficult to conduct a randomized controlled trial during post-marketing phase. If randomization is difficult, the applicant should explain the reason.

If surgical intervention is required at the time of administration, attention should be paid to the Hawthorne and positive placebo effects. For example, in the case of products requiring surgical intervention, it is assumed that for ethical reasons there may be some centers that are unable to perform the surgical procedure of the control group, and a prospective non-intervention control group and intervention product group may be established. If the control group data is collected retrospectively, inadequate development of the data base makes it difficult to interpret the results.

**(5) Blinding of assessments**

Blinding of assessments in use-results surveys, etc. may be difficult. However, if the evaluators do not know the patient's medical information with the attending physician, the assessment by the evaluators may be blinded. Therefore, it should be considered that an evaluator-blinded study should be performed in conjunction with standardization of assessment methods. An objective evaluation plan (e.g., evaluations by multiple physicians, evaluations by third-party) is appropriate. If an assessment is performed by the attending physician, the applicant must explain the necessity and validity of the assessment.

If the endpoints are not considered to be biased in the assessment, due to patients or evaluators subjectivity or differences between sites (e.g., mortality), and if appropriate external controls or existing data are available, a certain efficacy assessment may be possible in a use-results survey. In these cases, it does not need to be conducted as a blinded post-marketing clinical trial. On the other hand, even with such endpoints, if the number of events occurring is small, it may be difficult to accurately evaluate the efficacy. Therefore, in setting the primary endpoint, it is important to make an appropriate and evaluable plan taking into account the number of events occurring. It is also important to plan the evaluation of the efficacy of the product by comparing the key secondary endpoints with the control group. As a measure to ensure the objectivity of the evaluation, it is desirable to establish an independent central review committee for examining the validity of the evaluation in the use-results survey. If an independent central review committee is not established, the applicant should explain the reasons.

**(6) Setting of control group and method of data collection (prospective or retrospective)**

When post-marketing efficacy evaluation is conducted in non-randomized comparative use-results surveys, the issue of how to obtain data on subjects who do not use the product (control group), what types of biases occur, and how to deal with such data should be considered. Regarding these contents, the following points

should be noted.

1) Evaluation of efficacy based on scientific evidence requires "setting of control group" and "validity of endpoint to find difference from control group". In addition, if the level of evidence of efficacy at the time of conditional and time-limited approval is low, it will be difficult to verify the efficacy in the post-marketing approval condition assessment.
2) In order to evaluate the efficacy of regenerative medical products based on the results of use-results surveys, it is important to collect and utilize data on the clinical course of patients with the same disease background to determine the clinical course of patients without treatment with the product. In collecting information, it is necessary to note that the information obtained from different institutions and previous data are not necessarily appropriate because, in cases where the skill of the treatment procedure is relevant, the actual medical condition for the target disease and the disease background of the patient may differ depending on the institution, and in the data obtained by the results of the clinical trials and retrospective studies already conducted, the treatment system for the target disease may differ from the current or future treatment system. Therefore, it is appropriate to prospectively collect information on the clinical course of patients with the target disease who are candidates for the product at facilities where the product is to be administered, or at facilities considered equivalent, and to compare the results between the patients with and without the use of the product. If such a method cannot be adopted, the applicants should fully justify their method.
3) If a prognostic evaluation is performed, in principle, it is appropriate to set a randomized, control group. However, after conditional and time-limited approval of regenerative medical products, it is assumed that it will be difficult to conduct randomized controlled clinical trials. In such cases, an appropriate comparison with an external control should be planned. For the selection of a control, it is considered to be a plan to use a control for patients who do not use the regenerative medical product in the same facility who are considered to be receiving the equivalent treatment. However, if patient selection biases are concerned, such that the regenerative medical product tends to be used in patients in whom the product is available within the same institution and the control is biased toward patients who are not eligible for the product, then methods for selecting control patients from other institutions are also acceptable. In doing so, however, attention should be paid to the effects of differences between institutions. It is necessary to reduce biases in the efficacy evaluation by using methods such as matching of the patient background between patients included as controls and patients using the product.
4) When evaluating the efficacy of regenerative medical products by prospectively obtaining data at facilities that use and do not use those products, the following points should be noted:
    i. It is expected that the patient backgrounds are different because the facilities are different.
    ii. Special circumstances can be assumed, such as limited areas where products are supplied and limited facilities for use to comply with the Cartagena Act.
    iii. For products that are mass-produced before treatment and widely distributed (e.g.,

allogeneic cell-processed products), it is still difficult to collect prospectively post-marketing information on the course of patients who do not use the product if the requirements of the facilities and physicians that can be used are limited or if the product is highly expected.

iv. When surgical intervention is required at the time of administration, attention to the Hawthorne effect or positive placebo effect is warranted. Due to ethical concerns, the trial with non-intervention control and intervention treatment group may only be possible.

v. A large number of sites will facilitate the establishment of sites for which prospective control data will be obtained. However, it should be confirmed that standardized evaluations can be performed appropriately at all evaluation sites.

vi. Prospective data collection of control group should be performed over the entire data collection period of product group. This is because the efficacy of regenerative medical products may change due to the skill of the administration technique of the medical worker, convergence and change of the subject patient background based on the clinical experience, improvement in the condition management, etc. If the prospective data collection of control group is completed early in the data collection period of product group or within other specific period, the data of control group may become inappropriate as a control.

vii. If external controls are used in the efficacy evaluation, matching of comparative data can be accommodated for a small number of factors. With prognostic factors, it is difficult to match the prospective group in which the product is used with the retrospective control group, and adjustment using propensity score, etc. is required. Therefore, if prognostic factors need to be considered, it is desirable to obtain control data prospectively rather than retrospectively.

viii. Regenerative medical products that have been newly marketing approval often have strict requirements for facilities and physicians. Therefore, it may be difficult to obtain data prospectively in other hospitals with similar backgrounds. In such cases, consider whether it is possible to compare the data in the validated database or to compare it with retrospective historical control data at the same institution.

5) When the data of product group is prospectively taken and the data of control group is retrospectively taken, it is necessary to examine whether the data can be used, considering the reliability and continuity of the data and the effect of the historical background, etc. Use of a validated regenerative medicine data registry (e.g., NRMD https://nrmd.jp/ or FormsNet3 https://www.jdchct.or.jp/ctr/(Link)) could be considered as a means of obtaining data for control group. When retrospective control group data are obtained, it is necessary to confirm in advance that the necessary data for evaluation are obtained. It should be noted that the patient background and the data collection period may be different, or the subjects may be enrolled differently, the data may be essentially incomplete. It is usually necessary to examine whether the retrospective data and the prospective data can be assessed taking into account factors such as the fact that there

are several years between the time of acquisition and the advancement of supportive treatments and drugs and the method of rehabilitation. Considering that there is usually a difference of several years between when retrospective and prospective data were collected, and factors such as advances in supportive care, medicine, and rehabilitation methods, it is necessary to determine whether the data can be evaluated.

**(7) Methods for collecting post-marketing information**

There are limitations to the evaluation based on the use-results surveys. Even if the bias is eliminated to the maximum extent practicable, the results may be questionable. When evaluating the product after conditional and time-limited approval rather than through clinical trials, the following points should be noted regarding the issue of how to continuously provide information on the product profile after conditional and time-limited approval to medical professionals.

1) The severity of the target disease, the number of patients with the target disease, QOL of the patient, or the presence or absence of alternative therapies

   The degree of tolerance of biases in the data from use-results surveys may depends on the severity of the target disease, the number of patients with the target disease, QOL of the patient, and the presence or absence of alternative therapies. However, in general, allowing bias carries the risk of compromising the validity of the efficacy and safety evaluation.

2) System for post-marketing verification of mechanism of efficacy and the related critical quality attributes

   It is important to deepen understanding of the mechanism of action of the product and the relevant critical quality attributes by analyzing the post-marketing clinical experience and the product quality attribute data when they have not been fully demonstrated at the pre-marketing stage. Potential information available from analysis of post-marketing experience and product quality characteristic data may include, for example:

   i. Understanding the mechanism of action by correlation analysis between clinical efficacy and quality characteristic data
   ii. Confirmation of the validity of the critical quality attributes related to efficacy at the time of conditional and time-limited approval by correlation analysis between clinical efficacy and quality verification or data on manufacturing quality attributes.
   iii. Identification of novel critical quality attributes by correlation analysis between clinical efficacy and quality characteristic data
   iv. Pharmacokinetics or distribution of the product
   v. Understanding about patient groups with promising efficacy through clinical experience and stratified analyses of target diseases
   vi. Improving efficacy or reproducibility of treatment by improving and standardizing the clinical procedures of physicians and by combining them with rehabilitation, etc.

3) Feasibility of collecting efficacy evidence by the post-marketing approval condition assessment

In addition to the risk management plan for ensuring the safety of post-marketing products, the applicant should present a management plan for the risk that may not be able to achieve the collection of efficacy evidence suitable for scientific evaluation in the planned post-marketing approval condition assessment, and agree with the regulatory authorities prior to the conditional and time-limited approval, taking into account the elements and points listed in (1) to (7).