Provisional Translation (as of March 2025)*

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To: Directors of Prefectural Health Departments (Bureaus)

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

Guidance for Conditional and Time-Limited Approval for Regenerative Medical Products and the Development of Subsequent Efficacy Evaluation Plan

Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (PMD Act) provides conditional and time-limited approval for regenerative medical products to ensure safety and to seek rapid practical application (Article 23-26). Four products have been approved through conditional and time-limited approval scheme.

With the aim of increasing predictability of the application for the conditional and time-limited approval scheme and promoting the further development of regenerative medical products, the "Guidance for Conditional and Time-Limited Approval for Regenerative Medical Products and the Development of Subsequent Efficacy Evaluation Plan" has been compiled as attached. Please notify the related organizations under your jurisdiction of this Notification to utilize as a reference for the development of regenerative medical products.

In addition, the copy of this notification is released to related associations and Pharmaceuticals and Medical Devices Agency (PMDA).

Guidance for Conditional and Time-Limited Approval for Regenerative Medical Products and the Development of Subsequent Efficacy Evaluation Plan

1. Background

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."

Also in 2013, Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (PMD Act) (Act No. 145 of 1960), which revised the Pharmaceutical Affairs Law, was enacted. In the PMD Act, processed human cell products used in regenerative medicine (including *ex vivo* gene therapy) and *in vivo* gene therapy products were classified into the new category "regenerative medical products" (Article 2, paragraph (9)) that was independent of pharmaceuticals and medical devices, in order to achieve the practical use of regenerative medicine. Based on the characteristics of regenerative medical products, "conditional and time-limited approval scheme for regenerative medical products" (Article 23-26) [1] was newly established.

As of March 2023, four products have been approved through conditional and time-limited approval scheme. [2] The regulatory authorities (Pharmaceuticals and Medical Devices Agency (PMDA) and MHLW) decide whether marketing approval should be conditional and time-limited based on the marketing submission dossiers. The four products, which were approved through the conditional and time-limited approval schemes, have been reviewed on a case-by-case basis based on the marketing submission dossiers. However, cabinet council for development of regenerative

[1] Article 23-26 of the PMD Act (Conditional and Time-Limited Approval)
When an item that the applicant for approval prescribed in paragraph (1) of the preceding Article intends to market is a regenerative medical product which falls under all of the following items, the Minister of Health, Labour and Welfare (MHLW) may grant approval prescribed in paragraph (1) of the same Article for such item by providing necessary conditions for the appropriate use of the item with a period not exceeding seven years, not withstanding the provisions of paragraph (2), item (iii), (a) and (b) of the same Article, after obtaining opinions from the Pharmaceutical Affairs and Food Sanitation Council:
(i) the regenerative medical product pertaining to the application has heterogeneity;
(ii) the product is predicted to have the proposed indication or performance in the application;
(iii) It should not be predicted to be of no value for use as a regenerative medical product due to its markedly adverse effects compared with the indication or performance of the application.

[2] HeartSheet, Stemirac Injection, Collategene Intramuscular Injection 4 mg and Delytact Injection

medicine and cell and gene therapies as pointed that it is expected to ensure the predictability of conditional and time-limited approval.[3]

2. Objective

One of the requirements for conditional and time-limited approval of regenerative medical products is that the safety is confirmed and the efficacy can be predicted based on the results of clinical trials.

During a series of clinical developments, it is important to consider the following items based on an estimate of the benefits that the products will ultimately bring to patients.

- The certain efficacy information obtained from exploratory clinical trials in the early development stage
- The efficacy and safety information that can be obtained in post-marketing approval condition assessment

In other words, the marketing under conditional and time-limited approval should be understood as a process of the clinical development that leads to the full approval review and re-examination.

Therefore, developers of products which undergo clinical development through conditional and time-limited approval have to present a rational and feasible plan of post-marketing approval condition assessment for safety and efficacy evaluation towards full approval at the time of marketing application .[4]

In addition, for ensuring the sustainability of efficacy, safety, and quality of the products, it is important to further understand the background on the conditional and time-limited approval, such as the heterogeneity of the products, and to continue efforts to improve the reproducibility of the quality. It is recommended that the plan for these efforts be presented at the time of marketing application.

Appropriate operation is required based on the deep understanding of the conditional and time-limited approval scheme.

To increase the possibility of development of regenerative medical products subject to the conditional and time-limited approval scheme, this guidance provides the following items.

- Specific examples of the scope of application under the conditional and time-limited approval scheme
- Points to be considered for the development

[3] Interim Summary of the Discussion of the Cabinet Council for Development of Regenerative/cell Medicine and Gene Therapy (May 28, 2021)

[4] Technical Guidance for Quality, Nonclinical Safety Studies and Clinical Studies of Regenerative Medical Products (Human Cell-Processed Products) (Annex of PSEHB/MDED Administrative Notice, 2016) 4.6.2 Conditional and time-limited approval scheme and development lifecycle

- General principles regarding the following items that should be considered for obtaining the conditional and time-limited approval
    - The design of use-results survey or post-marketing clinical study conducted as post-marketing approval condition assessment
    - The plan for post-marketing efforts to ensure the sustainability of efficacy, safety, and quality of heterogeneous regenerative medical products

However, this guidance will be revised based on further technological innovations and knowledge accumulated in the future and will not be binding on the contents of marketing submission dossiers, etc. The developers should collect the required information flexibly with a thorough understanding of the specific characteristics of the products, in order to ensure a rational decision on conditional and time-limited approval and a rational review of post-marketing efficacy evaluation plan can be made.

It is recommended to consult with PMDA on the efficacy evaluation plan required for individual products. In addition to this guidance, other related guidelines of both domestic and international should also be referred.

3. Scope

Conditional and time-limited approval scheme for regenerative medical products allows MHLW to grant marketing approval with conditions and time limit to regenerative medical products of which the efficacy is predicted and safety is confirmed based on clinical trial data in the early development stage.

Regenerative medical products composed of cells, viruses, etc. are often heterogeneous in the quality, and it is important to confirm efficacy based on a clinical trial with a sufficient number of subjects. However, in many cases especially for rare diseases, it is required to evaluate the products in clinical trials with a limited number of subjects. In addition, considering the manufacturing capacity of the investigational products, innovative mechanism of action, the number of indicated patients, the clinical positioning of the products etc., it is concerned that it will take a long time to confirm the efficacy of the products based on clinical data and thus it will become difficult to deliver the products to patients awaiting treatment.

In particular, for patients with life-threatening disease and do not adequately respond to conventional treatments, long-term development of regenerative medical products that are expected to be effective may have a fatal effect.

In light of these considerations, conditional and time-limited approval scheme was established for the products of which the efficacy is predicted and safety is confirmed based on the result of clinical trials, on the premise that the products will be confirmed its efficacy, and further evaluated for safety after marketing, and re-application for full approval within the granted time-period. Developers should not set conditional and time-limited approval as a final goal of their development but should make a development plan including efficacy confirmation evaluation in advance. Developers should understand

that regulatory authorities will apply this conditional and time-limited approval scheme to the products based on the results of the exploratory studies conducted during the development.

Therefore, based on the background of the establishment of the conditional and time-limited approval scheme, developers wishing to increase the predictability of this approval should consider that this approval scheme is applicable to regenerative medical products that will meet all of the following 1) to 3).

If it is unclear whether the following 1) to 3) are applicable to the products (e.g, when using novel technologies), the developers are recommended to consult with PMDA and discuss whether the products are applicable to the conditional and time-limited approval scheme.

1) The regenerative medical product pertaining to the application has heterogeneity (Article 23-26, paragraph (1), item (i) of the PMD Act).

- The cell-processed products may be considered heterogeneous, because cells collected from humans are heterogeneous cell populations, and the characteristics of these cells change further by processing such as culture and differentiation, resulting in subpopulation.
- The products containing genes that are expressed in the body may be considered heterogeneous because the expression level of pharmacologically active substances may be heterogeneous.

2) The product is predicted to have the proposed indication or performance in the application (Article 23-26, paragraph (1), item (ii) of the PMD Act).

The efficacy of the product can be evaluated from appropriate clinical trial data, and the product is predicted to have the indication or performance pertaining to the application.

When conducting development plan with the application of this approval scheme, it is recommended to consult with PMDA in advance regarding clinical trial design. Even when predicting the efficacy, the clinical trial to be evaluated should be conducted with an appropriate design and operation, including endpoints with clinical significance, plan to minimize biases among evaluators, and reliability of the clinical trial.

Basically, efficacy should be assessed using established endpoints. However, if the endpoint has not been established, it is necessary to explain that the endpoint is expected to have clinical significance. It is easier to agree with PMDA in case clinical studies are designed to confirm efficacy trends in the overall populations based on pre-defined hypothesis. Therefore, it is important to set the success criterion statistically to determine to predict efficacy. See Tables 1 and 2 for typical methods of calculating the required subject numbers. Since the hypothesis based on endpoints need to be discussed on a case-by-case basis, depending on the characteristics of the products, disease, etc., it is desirable to agree on them in advance through consultation meeting with PMDA.

Table 1. Numbers of subjects required for the statistical test comparing the response rates between the two arms under the two-sided significance level of 10%, the power of 80%, and the 1:1 allocation (reference)

Randomized controlled trial		Response rate (Control group)								
		80%	70%	60%	50%	40%	30%	20%	10%	5%
Response rate (Treatment group)	90%	314	98	50	32	22	16	12	8	8
	80%	–	462	128	62	36	24	16	12	10
	70%	–	–	562	148	66	38	24	16	12
	60%	–	–	–	610	154	66	36	22	16
	50%	–	–	–	–	610	148	62	32	24
	40%	–	–	–	–	–	562	128	50	34
	30%	–	–	–	–	–	–	462	98	56
	20%	–	–	–	–	–	–	–	314	120
	10%	–	–	–	–	–	–	–	–	686

Table 2. Numbers of subjects required for the statistical test comparing the response rate of the single arm with the threshold under the two-sided significance level of 10% and the power of 80% (reference)

Single-arm trial		Response rate (Threshold)								
		80%	70%	60%	50%	40%	30%	20%	10%	5%
Response rate (Treatment group)	90%	83	26	13	8	5	3	−*	−*	−*
	80%	–	119	33	15	9	5	3	−*	−*
	70%	–	–	142	37	16	9	5	3	−*
	60%	–	–	–	153	38	16	8	4	−*
	50%	–	–	–	–	151	35	13	6	3
	40%	–	–	–	–	–	136	29	10	5
	30%	–	–	–	–	–	–	109	20	9
	20%	–	–	–	–	–	–	–	69	22
	10%	–	–	–	–	–	–	–	–	150

*Minimum required subjects are defined as ≧3 subjects in this study and therefore not shown in this table.

In the case of an exploratory assessment of whether the products are “predicted to have the indication or performance” retrospectively conducted based on previous clinical trials, it will be considered not only the results of the clinical trial, but also the rarity and severity of the target disease, as well as the lack of conventional treatments with sufficient efficacy, etc.

It is possible to discuss whether the products are “predicted to have the indication or performance” with the regulatory authorities in the following cases.

- A certain degree of clinically meaningful information is observed in some of the product-treated group compared with the natural history (including data from the literature and real world data (RWD), etc.) even after eliminating spontaneous improvement or biases such as rehabilitation.

- A certain degree of clinically meaningful prolongation of survival is observed in the product-treated group, although disease progression is rapid in highly lethal disease and survival is rarely prolonged.
- A certain degree of clinical meaningful information has been obtained on biomarkers or other indicators that are expected to correlate with established efficacy measures.
- Although trial-and-error process is needed to establish a method for regenerative medical products that involve surgical procedures, a certain degree of clinically meaningful information has been obtained.
- A certain degree of clinical meaningful information is obtained in the product-treated group despite progressive and irreversible disease that finally becomes unresponsive to administration of conventional pharmaceuticals as it progresses.

3) The product is not considered to lack value as a regenerative medical product due to its markedly adverse effect compared to the proposed indication or performance in the application (Article 23-26, paragraph (1), item (iii) of the PMD Act).

   This requirement is confirmed by the results of safety assessments based on appropriate clinical trial data.

4. Points to be considered for the review of conditional and time-limited approval for regenerative medical products and assessment of the plan for post-marketing approval condition assessment.

In "the Projects for preparing evaluation guidance for next-generation medical devices and cellular- and tissue-based products of FY 2022", points to be considered for the assessment of the plan for post-marketing approval condition assessment were discussed. Although the discussion was based on the characteristics common to human cell-processed products, the guidance[5] by the project may also be used as a reference for regenerative medical products other than human cell-processed products.

In the guidance, for example, points to be considered for post-marketing approval condition assessment include (1) sample size, (2) number of evaluation sites, (3) objectivity of endpoints, (4) randomization of cases, (5) blinding of assessments, and (6) setting control group and method of data collection (prospective or retrospective). In order to increase the probability of success in the study, the above points should be carefully considered keeping in mind that the efficacy of the products should be confirmed after the condition and time-limited approval.

Post-marketing approval condition assessment plan should be strictly designed to get expected results within granted time-period, and the developers are recommended to consult with PMDA. It should be noted that the guidance may not cover all regenerative medical products approved through conditional and time-limited approval scheme.

[5] 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 (PSB/MDED Notification No. 0329-4, dated March 29, 2024)

5. Conclusion

Conditional and time-limited approval scheme for regenerative medical products was established to provide early delivery of products to patients awaiting treatment. Conditional and time-limited approval will be expired if efficacy is not confirmed based on post-marketing approval condition assessment.

The developers intending to develop products under the conditional and time-limited approval scheme have to consider a rational and feasible plan for post-marketing approval condition assessment towards full approval. This plan has to be present at the time of marketing application.

The applied regenerative medical products must not undermine the dignity and trust of patients who expect to receive treatment as soon as possible under the conditional and time-limited approval scheme. With that understanding, this guidance has been developed to clarify the key points for regenerative medical products approved thorough conditional and time-limited approval scheme to obtain full approval finally, and to enable continuous patient access to such products.