Provisional Translation (as of November 2025)*

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To: Director of the Prefectural Health Department (Bureau)

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

Handling of the Conditional and Time-Limited Approval for Regenerative Medical Products

The Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (PMD Act) provides the conditional and time-limited approval scheme for regenerative medical products to ensure safety and to seek rapid practical application (Article 23-26). Thus far, regenerative medical products have been approved for the marketing authorization on the condition that necessary surveillance should be conducted after marketing authorization without requiring the confirmatory clinical trial results, based on individual assessments of each situation. The operation of the conditional and time-limited approval scheme has been described in the "Guidance for Conditional and Time-Limited Approval for Regenerative Medical Products and the Development of Subsequent Efficacy Evaluation Plan" (PSB/MDED Notification No. 0329-3, March 29, 2024) (the Guidance for Conditional Approval).

Based on the experience in consultations and reviews conducted by the Pharmaceuticals and Medical Devices Agency (PMDA), we have identified frequently asked questions regarding the conditional and time-limited approval scheme and have decided to handle the procedures of the marketing authorization application (MAA) as described below. Please be advised and ensure thorough dissemination of this information to relevant organizations and institutions under your jurisdiction, and provide appropriate guidance and strive for proper implementation.

Please note that this notification does not change the handling of application documents required for MAA of regenerative medicine product, as previously required.

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

1. Procedures for Application on the Conditional and Time-Limited Approval

(1) Pre-application consultation

Regarding MAA for regenerative medical products, "Guidelines for Applications for Marketing Authorization of Regenerative Medical Products "(PFSB Notification No.0812-30, August 12, 2014) outlines the procedures. There is no application category specifically tailored to the conditional and time-limited approval scheme, and applications fall under the category of applications for a new regenerative medical product based on Article 23-25, Paragraph 1 of PMD Act (Application Category 1-1; 1-1 Application). Furthermore, when applying for a full approval after the conditional and time-limited approval, the applications fall under the category of application for a new regenerative medical product to be resubmitted within the granted time-period after receiving the conditional and time-limited approval (Application Category 1-2; 1-2 Application).

When applying for 1-1 Application intended for the conditional and time-limited approval scheme, it is desirable to apply for the PMDA's "pre-application consultation for regenerative medical products" before the application in order to discuss the evaluation of the available clinical data, the application data packages required for MAA, and the appropriateness of the draft Regenerative Medicine Products Approval Conditions Evaluation Plan. Considering the need to submit the application as soon as possible after the completion of the clinical trial required for the application, it is anticipated that the consultation will be conducted at the stage when the clinical trial data enabling an evaluation of the efficacy and safety of the investigational product for the target disease can be presented.

This consultation provides advice on whether the investigational product falls under the scope of the conditional and time-limited approval scheme. Specifically, discussions will cover whether the clinical safety and efficacy risk-benefit balance can be appropriately evaluated based on clinical trial data, considering the severity of the target disease. It will also cover whether an appropriate evaluation plan is established for post-marketing data collection to confirm the efficacy and further safety of the product. The discussions will involve medical experts as necessary.

Refer to the Guidance for Conditional Approval for points to note regarding the formulation of post-marketing efficacy evaluation plans. Please note that during this consultation, detailed discussions regarding the draft Regenerative Medicine Products Approval Conditions Evaluation Plan may not be possible. If you wish to consult further on the details of the draft plan, apply for PMDA's “Pre-application consultation for regenerative mdical products (additional consultation)” or “Consultation on plans for post-approval clinical trials for regenerative medical products with conditional and time-limited approval.”

(2) 1-1 Application intended for the conditional and time-limited approval scheme and its review

1) In MAA, a draft of basic plan for evaluation of post-marketing approval conditions should be attached as part of risk analysis document. Refer to "Format of Regenerative Medical Products Basic Plan for Evaluation of Post-marketing Approval Conditions and Basic Plan for Post-marketing Surveillance" (PSEHB/MDED Notification No. 0323-1, March 23, 2020) (procedural notification) for the format of basic plan for evaluation of post-marketing approval conditions.
2) In the review process, the validity of the draft of basic plan for evaluating post-marketing approval conditions is confirmed, and safety and efficacy are evaluated on the assumption that the confirmed

plans will be properly implemented. In principle, all patients using the product of conditional and time-limited approval scheme are subject to the post-marketing approval conditions evaluation by enrolling into post-marketing surveillance, in accordance with Article 23-26, Paragraph 1 of PMD Act to ensure the implementation of this scheme.

2. Procedures after the Conditional and Time-Limited Approval

1) Use-results surveillance reports of regenerative medical products with the conditional and time-limited approval must be submitted within 2 months after the expiration date of each period within 1 year (or within the period specified by the Minister of MHLW for regenerative medical products which is specified by the Minister of MHLW) from the date specified by the Minister of MHLW at the time of marketing authorization approval of the regenerative medical product within the period specified in the conditional and time-limited approval scheme, pursuant to the provisions of Article 23-26, Paragraph 3 of of PMD Act. Refer to "Instructions of Surveillance and Reexamination of Regenerative Medical Products Use-Results Surveillance " (PSEHB/MDED Notification No. 0328-1, March 28, 2022).
2) Consult with PMDA beforehand when changing the contents of the post-marketing approval condition evaluation plan based on trends of malfunctions in post-marketing, changes in the actual treatment of the target disease, and accumulation of post-marketing data.
3) It is desirable to thoroughly consider the handling of collected data and collection plans, including the utilization of data, so that the data collected in post-marketing of regenerative medical products covered by the conditional and time-limited approval scheme will be useful for future development and MAA of other regenerative medical products.
4) In principle, all patients using the product of conditional and time-limited approval scheme will be evaluated for post-marketing approval conditions. Even after the registration of patients subject to evaluation of post-marketing approval conditions has been completed, use-results surveillance should be conducted on all patients using the product until the decision will be made on the 1-2 Application. Regarding the plan of this use-results surveillance, consult with PMDA at the time of 1-1 Application. Additionally, consult with PMDA regarding the cut-off of data before 1-2 Application.
5) The granted time-period for regenerative medical products approved under the conditional and time-limited approval scheme may be extended for up to 3 years in accordance with Article 23-26, Paragraph 2 of PMD Act, after hearing the opinions of the Pharmaceutical Affairs Council when it is deemed particularly necessary for conducting proper review. Consult with PMDA on the need for extension at least six months before the deadline of the granted time-period.
6) In accordance with Article 23-25, Paragraph 11 of the PMD Act, which applies mutatis Article 23-26, Paragraph 4, partial changes must be approved by MHLW. This procedure is the same as in regenerative medical products with standard approval, but the granted time-period given by the 1-1 Application is maintained even after the partial changes have been approved. However, in regenerative medical products with the conditional and time-limited approval, since 1-2 Application must be submitted within the granted-time-period, applications for additional indications are to submit another 1-1 Application, because it should be evaluated separetaly from the evaluation of post-marketing approval conditions. In this case, conditions and period under the conditional and time-

limited approval scheme will be granted separately because the application will be different from the previous application. In light of the contents of the previous application, consult with PMDA to determine whether 1-1 Application is required.

3. Procedures of Appplicaiton after the Conditional and Time-Limied Approval

(1) 1-2 Application and Review

In accordance with Article 23-26, Paragraph 5 of PMD Act, regenrateive medical products that had received conditional and time-limited approval must be approved again within the granted time-period. In the application for approval, a draft of basic plan for post-marketing surveillance should be attached as part of the risk analysis document. Refer to the procedural notification for the format of the basic plan for post-marketing surveillance. Even if partial changes are planned at the same time, MAA must be submited separately. If you wish to consult with PMDA about the appropriateness of application data compilation and whether the demonstration of efficacy and further confirmation of safety of the product against target diseases have been made based on the data collected as evaluation of post-marketing approval conditions prior to the application, apply for PMDA's "Consultation at completion of clinical trials for regenerative medical product after the conditional time-limited authorization."

(2) Effect of the Conditional and Time-Limited Approval

If a 1-2 Application is submitted pursuant to the provisions of Article 23-26, Paragraph 5 of PMD Act, and if the decision is not made for the application within the granted time-period, the approval under Article 23-25, Paragraph 1 of PMD Act with condition and time-limet set pursuant to the provisions of Article 23-26, Paragraph 1 of PMD Act shall remain in effect after the expiry of the granted time-period until the disposition is made.

In the case of a 1-2 Application pursuant to the provisions of Article 23-26, Paragraph 5 of PMD Act, PMDA shall review the contents of the application, compile the review report, and deliberate on the approvals at the Pharmaceutical Affairs Council of MHLW. As a result, an approval under Article 23-25, Paragraph 1 of PMD Act is deemed acceptable, the Minister of MHLW shall notify the prefectural government of the results of the deliberation and issue a notification of approval to the applicant. At this point, the conditional and time-limited approvals expire and the approval under Article 23-25, Parageraph 1 of PMD Act is granted again.

On the other hand, in the case of the approval under Article 23-25, Paragraph 1 of PMD Act is denied as a result of deliberation, the Minister of MHLW shall issue a notification of disapproval to the applicant after completing the necessary procedures in accordance with the Administrative Procedure Law (Law No. 88 of 1993) and notify the prefectural government of the result of deliberation. The effect of conditional and time-limited approval in this case are described as follows.

1) If the period of conditaional and time-limited approval has passed prior to the date of issuance of the notification of disapproval, the conditional and time-limited approval expires upon the issuance of the notice in accordance with Article 23-26, Paragraph 6 of PMD Act.
2) If the period of conditaional and time-limited approval has fallen after the date of issuance of the notification of disapproval, the conditional and time-limited approval shall remain effective until the expiration date. Therefore, if the conditional and time-limited approval have not yet expired as of the

date of the MHLW Pharmaceutical Affairs Council, which discusses the approvals in Article 23-25, Paragraph 1 of PMD Act, and if the approval is not granted as a result of deliberations, it is necessary to continue to deliberate on whether to maintain the conditional and time-limted approval. As a result, if it is determined that the regenerative medical product no longer falls under Article 23-26, Paragraph 1, Item 2 or Item 3 of the PMD Act, the conditional and time-limited approval shall be revoked pursuant to the provisions of Article 74-2, Paragraph 1 of the PMD Act, following the necessary procedures under the Administrative Procedure Law.

3) Furthermore, if the approval under Article 23-25, Paragraph 1 of the PMD Act is not granted as a result of deliberation, it is desirable to continue ongoing surveillance and collect safety-related information for patients who have received the regenerative medical product subject to the application.

(3) Use-results surveillance

After a 1-2 Application is submitted pursuant to the provisions of Article 23-26, Paragraph 5 of the PMD Act, and approval is granted under Article 23-25, Paragraph 1 of the PMD Act, it is necessary to conduct use-results surveillance for re-examination of the product. In addition, the use-results surveillance should be conducted on patients who used the product after the 1-2 Application. It should be noted that the data that could not be submitted in 1-2 Application must be submitted at the time of the application for re-examination.

(4) Handling of Review Report

Conditional and time-limited approval scheme expects patients to have early access to regenerative medical products with predicted efficacy at an early stage of the clinical trial, while marketing authorization holders are required to fully respect the wishes and dignity of those institutions or patients who have received regenerative medical products approved under the conditional and time-limited approval scheme because the products of which efficacy has not yet been sufficiently demonstrated will be marketed and administered to patients. Therefore, it is extremely important to demonstrate the efficacy of the in the evaluation of post-marketing approval conditions and to publicize the results. Thus, even if the marketing authorization holder submits the withdrawal of the application or the approval withdrawal notification of the product to the administrative agency after the application is submitted again pursuant to the provisions of Article 23-26, Paragraph 5 of the PMD Act, PMDA shall review the study results collected by the marketing authorization holder before the deadline of the granted time-period, compile the review report, and publish the review report.

4. Basic Approach Regarding the Utilization of the Conditional and Time-Limited Approval Scheme and Japanese Clinical Data in Cases Where Clinical Trials of Regenerative Medical Products for Rare Diseases, etc., Have Been Conducted Only Overseas

In Japanese approval review process for regenerative medical products, the basic approach is to evaluate the efficacy and safety in Japanese patients under Japanese healthcare environment based on the results of multi-regional clinical trials in which Japan participated or domestic clinical trials. For multi-regional clinical trials, even if the number of Japanese patients enrolled in the trial is very small, it is possible to compare the Japanese patients' results of the study with those of the overall results based on a

comprehensive and multifaceted evaluation from a clinical perspective. In addition, from the viewpoint of providing information to medical institutions, participation of Japan is of significance, and it is important that Japan also participate to the greatest extent possible.

However, with regard to regenerative medical products which clinical development is progressing overseas, conducting new clinical trials in Japan may further delay the access to the regenerative medical products for Japanese patients. There are also cases in which the development in Japan is delayed due to the additional Japanese clinical trials being required by the regulatory authority.

To ensure the efficacy and safety in Japanese patients while minimizing the disadvantage of delayed or lost access to regenerative medical products for Japanese patients due to the additional clinical trials, we will actively consider utilizing the conditional and time-limited approval scheme for the products, that:

- have approval in countries that have approval schemes equivalent to Japan, such as EU and the United States, or have plans for simultaneous applications in Japan and these countries
- have concrete plans that can be presented and executed to collect and evaluate post-marketing data toward 1-2 Application within the granted time-period to confirm the efficacy and safety of the product after approval, including confirmatory trials (including those for different treatment lines).

In addition, the following summarize the cases where it is considered possible to apply for 1-1 Application intended for the conditional and time-limited approval scheme without clinical trial results in Japanese patients.

(1) If the products meet all of the following 1) to 3), it may be possible to submit 1-1 Application intended for the conditional and time-limited approval scheme without clinical trial results in Japanese patients. This is not necessarily limited to the case.

1) When a clinical trial that serve as primary evaluation has been appropriately conducted overseas (including when the relevant interim analysis has been completed. if the primary evaluation is available in the interim analysis)

   However, if regenerative medical products have been approved overseas based on case reports and real-world evidence rather than the result of clinical trials, the clinical trials of the products do not need to be completed overseas.

2) When it is difficult to conduct a new clinical trial in Japan due to the extremely small number of patients

   The difficulty of conducting clinical trials is not necessarily judged solely by the number of patients, but is also judged comprehensively based on the characteristics of indicated diseases such as seriousness, high unmet medical needs. For example, in cases of life-threatening diseases or rapidly irreversible progressive diseases, it may be difficult to conduct clinical trials regardless of patient numbers, because of the significant disadvantage to patients caused by the considerable amount of time for regenerative medical products to be approved with clinical trials conducted in Japan, even considering the uncertainty due to the lack of efficacy and safety data in Japanese patients.

3) When it is predicted to be beneficial to Japanese patients comprehensively based on the available information on efficacy and safety

(2) However, if the characteristics of the regenerative medical product and the information from similar

products specifically suggest clinically significant ethnic difference between non-Japanese and Japanese patients, or if the data on ethnic difference is insufficient, additional information to evaluate the safety or appropriateness of the dosage may be required. In such cases, the results of clinical trials in Japanese patients may be considered necessary at the time of 1-1 Application.

5. Concept of Quality Control Strategy throughout Product Life Cycle

Regenerative medical products, like pharmaceutical products, should develop quality control strategy that involves understanding quality risk, including identifying and understanding the critical quality attributes of the product and identifying and controlling the critical process parameters. The GCTP considers the use of quality risk management, and the use of quality risk management should promote understanding of product quality and manufacturing process to achieve higher quality assurance. Furthermore, rather than simply ensuring quality through specifications, it is important to establish a holistic control strategy based on an understanding of product quality and manufacturing process and quality risk management to ensure that a product of desired quality will be produced consistently by controlling from upstream to downstream of the manufacturing process and from raw materials to final product.

In addition, a development strategy that considers the differences in responses at each stage of the product life cycle is required. It is important to establish quality control strategy through quality risk management based on the understanding of the product quality and manufacturing process obtained at the time, taking into full consideration that the manufacturing process and analytical procedures have not yet been established in the development stage in the manufacture of the investigational product. It may not be possible to adequately identify process parameters, raw materials, and other variables when just multiple repetitions are conducted at the time of obtaining conditional and time-limited approval, and it may not be possible to consistently produce a product that meet the desired quality. Therefore, it may be necessary to confirm that a product of the desired quality have been obtained through verification. It is important to establish a flexible control strategy based on scientific and quality risk in accordance with the development stage to ensure quality. It is also desirable to take measures such as accumulating necessary information through appropriate use of verification and other methods, and utilizing the information for control for full approval.

Where a conditional and time-limited approval is granted, quality control strategy developed at a relatively early stage of clinical development based on an understanding of product quality and manufacturing experience obtained at that stage may be provisional. In accordance with GCTP, it is important to continuously improve the quality control strategy, including the establishment of quality control items that may become critical quality attributes and process parameters by considering the application of quality risk management throughout the product lifecycle at the manufacturing site. This improvement should incorporate knowledge gained from accumulated manufacturing experience through the efforts of product quality review, as well as additional knowledge about quality attributes obtained after the conditional and time-limited approval.