Practical Guide to the Conditional and Time-Limited Approval Scheme for Regenerative Medical Products in Japan

Introduction

Regenerative medical products are defined as products that consist of processed human or animal cells intended for (1) reconstruction, repair, or formation of the structure or function of the human body, or (2) treatment or prevention of disease, as well as products containing genes introduced into human or animal cells for expression in the body and intended for the treatment of disease. These products are expected to provide innovative therapeutic options for serious and intractable diseases. On the other hand, it has been noted that regenerative medical products are often heterogeneous because cells or genes are used as starting materials, and that factors other than the products themselves, such as physicians' methods and techniques of use and postoperative management, may also have a non-negligible impact on treatment outcomes, making it difficult to clearly distinguish the effects attributable to the performance of the products themselves.

The conditional and time-limited approval scheme for regenerative medical products (the Scheme) was newly established in 2014 and has been operated as a framework that supports the early practical application of regenerative medical products and timely patient access. At the same time, this scheme was not established merely as an exceptional mechanism for accelerating the timing of approval. In light of the aforementioned unique characteristics of regenerative medical products and the challenges associated with their development, the Scheme was established on the premise that products for which safety has been confirmed and efficacy is presumed based on the results of clinical trials may be granted conditional and time-limited approval, followed by verification of efficacy and further evaluation of safety after marketing, and that a new application must be submitted within the specified approval period.

Thus, conditional and time-limited approval is not intended to constitute the final stage of product development or evidence generation. Rather, generation of evidence sufficient to support full approval through post-approval evaluation is an essential prerequisite for the operation of the scheme. The cases of HeartSheet and Collategene Intramuscular Injection 4 mg, which did not ultimately obtain full approval and were discontinued, underscore the importance of development plans and implementation schemes that anticipate post-approval evaluation when using this scheme. Even if efficacy is presumed at the time of approval, continuation of the approval cannot be permitted if evidence sufficient for full approval cannot be generated after approval. Sponsors considering use of this scheme should therefore

carefully examine evaluation plans not only for obtaining initial approval but also for transition to full approval.

Based on the experience gained to date and the discussions held when the scheme was established, this document has been prepared and edited by the Forum for Innovative Regenerative Medicine (FIRM). It is intended to organize and disseminate, for sponsors involved in the development or marketing authorization of regenerative medical products, the overview of this scheme, relevant notifications and guidance, case examples, and practical considerations.

1. Background to the Establishment and Purpose of the Scheme

The conditional and time-limited approval scheme for regenerative medical products was established to facilitate the rapid practical application of regenerative medical products and thereby provide patients with timely access to treatment, while ensuring safety and taking into account the specific characteristics of such products.

The legal framework for the Scheme was established through the 2013 amendment of the Pharmaceuticals, Medical Devices, and Other Therapeutic Products Act (PMD Act), namely the amendment that led to the current Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. This amendment established regenerative medical products as a new product category alongside pharmaceuticals and medical devices and introduced an approval framework tailored to their characteristics.

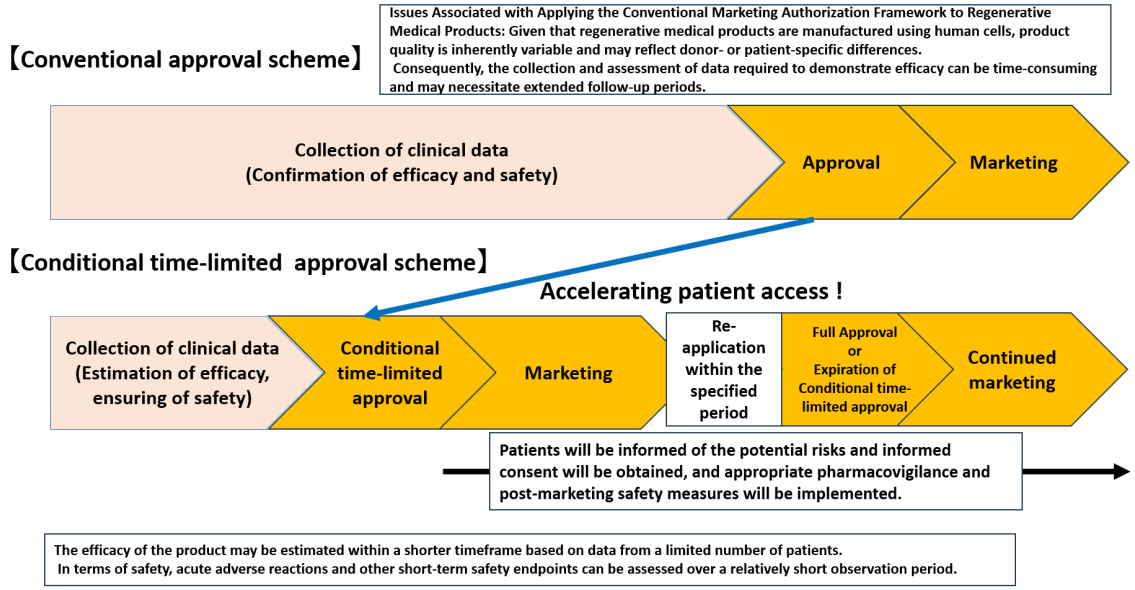
The Schem was established against the background of the difficulty in evaluating the efficacy of regenerative medical products arising from their inherent heterogeneity and other product-specific characteristics. Regenerative medical products that use cells or genes may be affected by the condition of the source cells and by culture or processing steps and therefore may be difficult to evaluate as homogeneous products in the same manner as conventional small-molecule pharmaceuticals. Consequently, enrolling a sufficient number of patients to statistically confirm efficacy may require a prolonged period of time. Conversely, where the target disease is serious and existing therapies do not provide adequate benefit, prolonged development itself may constitute a significant disadvantage for patients. The Scheme was established as a mechanism to reconcile early patient access with assurance of safety.

Under the Scheme, marketing authorization may be granted with conditions and within a specified period when certain requirements are met for heterogeneous regenerative medical products. The PMD Act provides that approval may be granted with conditions necessary to ensure proper use and with a time limit not exceeding seven years for regenerative medical products that satisfy all of the following: the products pertaining to the application have heterogeneity; the product is presumed to have efficacy, effects or performance pertaining to

the application; and the item pertaining to an application is deemed as not being of value as a regenerative medicine product pertaining to an application due to its significantly harmful action for its efficacy or performance (see Section 2.2). The holder of such approval must submit a further application for full approval within the specified period, attaching materials on use results and other relevant data. Importantly, the Scheme does not eliminate the need to confirm efficacy and safety required for full approval under Article 23-25 paragraph 1 of the PMD Act. Rather, based on limited clinical data, it permits initial marketing authorization with conditions and a time limit where a certain level of efficacy is predicted and safety is confirmed. Thereafter, data must be collected systematically after marketing, efficacy verified, safety further evaluated, and a new approval application (Application Category 1-2, hereinafter referred to as a “1-2 application”) submitted within the time limit (see Figure 1).

This point is essential to understanding the basic concept of the Scheme. 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, 2024 states that marketing under the 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. The guidance also states that 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 evaluation for safety and efficacy evaluation towards full approval at the time of marketing application. The guidance further clarifies that development sponsors should not design development plans with conditional and time-limited approval as the final objective but should plan in advance through verification of efficacy.

As described above, the scheme was established to enable patients to gain early access to regenerative medical products at a stage when a certain degree of efficacy can be inferred and safety has been confirmed, taking into account factors such as the heterogeneity of such products, the seriousness of the target diseases, and the difficulty of enrolling a sufficient number of patients. At the same time, the scheme is predicated on the verification of efficacy and safety in the post-marketing setting and the submission of a “1-2 application” within the specified period. In other words, conditional and time-limited approval is not the ultimate goal of the scheme; rather, the scheme is intended to ultimately lead to full approval. Conditional and time-limited approval should therefore be regarded as an intermediate stage in clinical development toward full approval.



Reference：https://www.mhlw.go.jp/file/06-Seisakujouhou-11120000-Iyakushokuhinkyoku/0000066816.pdf

Figure 1. Overview of the Conditional and Time-Limited Approval Scheme for Regenerative Medical Products

As of September 2026, more than 20 regenerative medical products had been approved in Japan, of which eight had received conditional and time-limited approval, with six currently remaining approved. Heart Sheet and Collategene Intramuscular Injection 4 mg submitted applications toward full approval but did not obtain full approval and were discontinued through administrative discontinuation or withdrawal. These developments further demonstrate that conditional and time-limited approval is not the final destination, but an interim and provisional approval framework that institutionally requires additional evidence generation and verification toward full approval.

Table 1. Regenerative Medical Products Granted Conditional and Time-Limited Approval (as of September 2026)

Brand name	Nonproprietary name	Product category	(1) Approval date(Y/M/D) (2) Approval period (from approval)	Indication, efficacy or performance
HeartSheet	Human (autologous) skeletal muscle-derived cell sheet	Human somatic stem cell-processed product	(1) 2015/9/18 (2) 5 years + 3 years [*1]	Treatment of patients with severe heart failure due to ischemic heart disease unresponsive to standard treatments including drug and invasive therapies who meet all of the following criteria. - NYHA class III or IV heart failure; and - Resting left ventricular ejection fraction of 35% or less at rest
Collategene Intramuscular Injection 4 mg	Beperminogene Perplasmid	Plasmid vector product	(1) 2019/3/26 (2) 5 years [*2]	Improvement of ulcers in patients with chronic arterial occlusive disease (arteriosclerosis obliterans and Buerger's disease) who do not respond adequately to standard drug therapy and are poor candidates for revascularization
Stemirac for Injection	Human (autologous) bone marrow-derived mesenchymal stem cells	Human-derived somatic stem cell product	(1) 2018/12/28 (2) 7 years[*3]	Improvement of neurological symptoms and functional disorders associated with spinal cord injury only in patients with traumatic spinal cord injury assessed as American Spinal Injury Association Impairment Scale (AIS) grade A, B or C
Delytact Injection	Teserpaturev	Gene expression therapy product	(1) 2021/6/11 (2) 7 years	Malignant glioma
AKUUGO Suspension for Intracerebral Implantation	Vandefitemcel	Human somatic stem cell-processed product	(1) 2024/7/31; 2025/12/8 [*4] (2) 7 years	Improvement of chronic motor paralysis associated with traumatic brain injury

ELEVIDYS for Intravenous Infusion	Delandistrogene moxeparvovec	Viral vector product	(1) 2025/5/13 (2) 3 years	Duchenne muscular dystrophy exclusively meeting all of the following criteria: - Anti-rAAVrh74 antibody-negative patients - Ambulatory patients - Patients aged 3 years to less than 8 years
RiHEART	Human (allogeneic) iPS cell-derived cardiomyocyte sheet	Human induced pluripotent stem cell-processed product	(1) 2026/3/6 (2) 7 years	Treatment of severe heart failure associated with ischemic cardiomyopathy that has an inadequate response to standard-of-care therapies, including pharmacotherapy and invasive interventions
AMCHEPRY	Ragneprocel	Human induced pluripotent stem cell-processed product	(1) 2026/3/6 (2) 7 years	Improvement of motor symptoms in patients with Parkinson's disease who have an inadequate response to conventional pharmacotherapies, including levodopa-containing drug products

Note 1: At the time of conditional and time-limited approval, the approval period was five years; however, in January 2019, the approval period was extended by three years, resulting in a total period of eight years (see Section 2.6, item 5). A further approval application (1-2 application) under Article 23-26, to be submitted again within the specified time limit after receiving conditional and time-limited approval, was submitted on September 7, 2023. On July 24, 2024, the application was determined not to be approvable, and sales were discontinued.

Note 2: A further approval application (1-2 application) under Article 23-26 was submitted on May 31, 2023; however, the application was withdrawn on June 27, 2024, and sales were discontinued.

Note 3: A further approval application (1-2 application) under Article 23-26 was submitted on November 14, 2025. Even if the period of conditional and time-limited approval expires after submission of the further approval application (1-2 application), the conditional and time-limited approval remains effective until a disposition is made on the further approval application (1-2 application).

Note 4: Date of approval of a partial change. As a result of this approval, one of the four approval conditions, “In view of the limited manufacturing experience with the product, the applicant is required to promptly collect information about the product’s quality according to the plan, evaluate quality

comparability between the product and the study product, and report the results. Based on these results, the applicant should file necessary partial change application. The product must not be shipped before the approval of the partial change application" was determined to have been addressed and was deleted from the approval conditions. The other three approval conditions remain unchanged. Marketing of this product commenced in May 2026.

2. Guidance and Notifications

2.1 Introduction

For matters to be considered in seeking application of the Scheme, and for the basic approach to the evaluation of efficacy and safety in post-marketing approval-condition evaluation toward conventional marketing authorization review, reference should be made to the MHLW notification entitled "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), dated March 29, 2024. The explanations in Section 2.2. are based on this notification.

The requirements for marketing authorization applications for regenerative medical products are set forth in the "Applications for Marketing Approval of Regenerative Medical Products'" (PFSB Notification No. 0812-30, dated August 12, 2014/Partial revision: March 31,2026).

For applications intended to obtain conditional and time-limited approval, the notification "Handling of the Conditional and Time-Limited Approval for Regenerative Medical Products", (PSB/MDED Notification No.1006-1), dated October 6, 2025 should also be consulted. Sections 2.3 through 2.7 are explained in accordance with these notifications.

2.2 Products Eligible for Conditional and Time-Limited Approval

Article 23-26, paragraph 1 of the PMD Act defines the scope of the Scheme as regenerative medical products that satisfy all of the following: the regenerative medical products pertaining to the application has heterogeneity; the product is predicted to have the proposed indication or performance in the application; and 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.

With respect to the requirement that the product has heterogeneity, for example, 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 subpopulations. As another example, 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.

With respect to the requirement that the product is predicted to have the proposed indication or performance in the application, sponsors developing a product with the Scheme in mind should consult PMDA regarding the appropriateness of the clinical trial design. Agreement with PMDA may be more readily reached where a clinical study is designed to assess an efficacy trend in the overall populations based on a prespecified hypothesis. Therefore, it is important to set the success criterion statistically to determine to predict efficacy. Where an exploratory post hoc assessment is made based on completed studies, clinical trial results should be considered together with factors such as the rarity and severity of the target disease and the absence of established therapies with sufficient effect. 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 clinically 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 clinically 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.

With respect to the requirement that 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, this refers to products for which safety can be confirmed based on appropriate clinical trial data and, as a result, the product is not considered to fall within that exclusion.

2.3 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 the review of regenerative medical products in Japan, the basic principle is to evaluate efficacy and safety in Japanese patients under the Japanese medical environment based on the results of a multi-regional clinical trial in which Japan participated or the results of a domestic clinical trial. However, for regenerative medical products for which clinical development has progressed overseas, to minimize the potential disadvantage to Japanese patients arising from delayed or lost access to regenerative medical products due to the conduct of additional clinical trials, use of the scheme may be considered when certain conditions are met. This approach may apply to products that have already been approved in a country with an approval scheme comparable to that of Japan, such as the United States or a European country, or for which simultaneous marketing authorization applications in such a country and Japan are planned. The applicant must also be able to present and implement a specific and appropriate plan for post-marketing data collection and evaluation. The plan must be designed to confirm efficacy and safety through a confirmatory trial or other means within the specified period following conditional and time-limited approval, with a view to submitting a 1-2 application.

On this basis, where all of the following conditions (Items 1 through 3) are met, it may be possible to submit an application for marketing authorization of a new regenerative medical product intended to seek conditional and time-limited approval, namely a “Category 1-1 marketing authorization application,” even in the absence of clinical trial results in Japanese patients.

1. When a clinical trial that serves as primary evaluation has been appropriately conducted overseas (including cases in which the relevant interim analysis has been completed and the primary evaluation is available from that interim analysis). A clinical trial serving as the primary basis for evaluation has been appropriately conducted overseas. However, for a regenerative medical product that has already been approved overseas on the basis of case reports, real-world evidence, or other evidence rather than clinical trial data, completion of an overseas clinical trial is not necessarily required.

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.

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

Even if all of the above conditions (Items 1 through 3) are satisfied, 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 initial application for conditional and time-limited approval (“1-1 application”).

When submitting a marketing authorization application intended to obtain conditional and time-limited approval, applicants are advised to consult the PMDA before submission regarding the need for clinical trial results in Japanese patients.

2.4 Approach to Quality Control Strategy

It is necessary to deepen the understanding of quality risks and to establish a quality control strategy that includes identification and understanding of critical quality attributes of the investigational product, as well as identification and control of the associated critical process parameters. It is also important to establish a scientifically sound, quality risk-based, and flexible control strategy according to the development stage, and to appropriately use approaches such as verification so that information necessary for full approval can be accumulated and used for control.

Where conditional and time-limited approval is applied, the marketing authorization application may be submitted at a relatively early stage of clinical development, and the quality control strategy established based on the product-quality understanding and manufacturing experience available at that time may be provisional. At the time conditional and time-limited approval is obtained, variability factors such as process parameters and raw materials may not yet have been sufficiently identified, and it may not be possible to state that products meeting the intended quality can be consistently manufactured. In such cases, verification may be necessary to confirm that products of the expected quality have been obtained.

Based on the GCTP standards, it is important to continuously improve the quality control strategy, including the establishment of quality control items and process parameters that may constitute critical quality attributes, by managing quality risks throughout the product

lifecycle at manufacturing sites and by considering both knowledge gained from manufacturing experience accumulated through activities such as product quality review and additional knowledge on quality attributes obtained after conditional and time-limited approval.

2.5 Procedures for Applications Concerning Conditional and Time-Limited Approval

When submitting an initial application intended for the Scheme (1-1 application), it is advisable to request PMDA's pre-application consultation for regenerative medical products once the sponsor considers that clinical trial data, a draft post-marketing approval-condition evaluation plan for the regenerative medical product or other data enabling evaluation of the product's efficacy and safety can be presented.

In such consultation, discussions may include whether the benefit-risk balance of safety and efficacy can be appropriately evaluated based on clinical trial data and other information, and whether the evaluation plan for data collection after marketing to verify efficacy and confirm safety is appropriate. Advice may also be obtained on whether the product falls within the scope of the Scheme. Where necessary, discussions may involve medical experts through expert consultation.

It should be noted that the details of the draft post-marketing approval-condition evaluation plan for a regenerative medical product may not be discussed fully during this consultation. Therefore, a sponsor wishing to seek further advice on the details of the draft post-marketing approval-condition evaluation plan for a regenerative medical product, should request either PMDA's additional pre-application consultation or consultation on post-approval clinical trial or other plans following conditional and time-limited approval.

Table 2. PMDA Consultations Available for Marketing Authorization Applications Intended to Use the Conditional and Time-Limited Approval Scheme

Consultation category	Description	Fee (JPY)
Regenerative medical product: preliminary meeting	A preliminary meeting is held in advance to organize the items to be discussed so that the face-to-face advice can proceed smoothly. Evaluation of data is carried out at the face-to-face advice meeting and is not done at the preliminary meeting. In a preliminary meeting for regenerative medical products, the (planned) review schedule for the marketing application may also be	- With record: 99,200 - Without record: free

	confirmed. If the applicant so requests, a record of the preliminary meeting is prepared for a fee.	
Regenerative medical product: pre-application consultation	Consultation in which advice and guidance are given for the first time, based on the clinical trial results obtained to date, on how to compile the application materials and on the adequacy of the materials, when preparing the materials for a marketing application.	- 3,684,200
Regenerative medical product: consultation on post-marketing studies following conditional and time-limited approval	Consultation in which advice and guidance are given for the first time, based on the clinical trial results obtained to date and information on similar products, regarding the plan for post-approval surveillance and post-marketing clinical studies, either after obtaining approval with conditions and a time limit or before application assuming such approval. Also covers first-time advice and guidance on changes to the surveillance plan or study plan during the period of the conditional, time-limited approval.	- With clinical study plan: 1,687,200 - Surveillance only: 1,266,400
Regenerative medical product: consultation at the completion of post-approval clinical trials and other studies following conditional and time-limited approval	A consultation provided for the first time to give guidance and advice on how to compile application dossiers and the sufficiency of such dossiers, based on the results of surveys and clinical trials conducted to date, when preparing application dossiers for the next marketing authorization application following conditional and time-limited approval.	- With clinical study plan: 1,687,200 - Surveillance only: 1,266,400
Regenerative medical product: additional consultation	A second or subsequent consultation held before the application after a pre-application consultation, or a second or subsequent consultation held after a consultation on post-marketing clinical study plans and before the end of the post-marketing clinical study.	- Pre-application consultation: 1,842,000 - Post-marketing clinical study plan consultation (with clinical study plan): 844,200 - Post-marketing clinical study plan consultation

		(surveillance only): 633,000
Regenerative medical product: follow-up consultation after face-to-face advice	Consultation held on additional matters (not involving evaluation of new data) that both PMDA and the applicant agreed, during a PMDA consultation on a regenerative medical product, could be handled in a follow-up consultation. If the applicant so requests, a record of the preliminary meeting is prepared for a fee.	- With record: 99,200 - Without record: free

Reference：
https://www.pmda.go.jp/review-services/f2f-pre/consultations/0035.html
https://www.pmda.go.jp/review-services/f2f-pre/consultations/0027.html
https://www.pmda.go.jp/review-services/f2f-pre/consultations/0030.html

At the time of application, a draft of basic plan for evaluation of post-marketing approval-condition 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.

In addition, because a notification concerning risk management plans for regenerative medical products is expected to be issued in the future, that notification should also be consulted once issued.

Marketing under conditional and time-limited approval should be appropriately regarded as part of the clinical development process leading to subsequent full approval review and re-examination. Accordingly, in clinical development involving conditional and time-limited approval, a rational and feasible plan for evaluating efficacy and safety in post-marketing approval-condition evaluation toward full approval must be presented at the time of the marketing authorization application.

Items to be considered in post-marketing approval-condition evaluation 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). An evaluation plan should be developed with reference to the guidance entitled “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).

From the outset of planning the post-marketing approval-condition evaluation, the evaluation plan should be developed with the confirmation of the product's efficacy in mind. Furthermore, when submitting a 1-2 application following conditional and time-limited approval, a thorough assessment should be conducted based on the results of the post-marketing approval-condition evaluation and other relevant information. If efficacy is not confirmed as a result of that evaluation, continuation of approval will not be permitted. In order not to undermine the dignity and trust of patients who have expectations for products granted conditional and time-limited approval, it is important to develop an evaluation plan capable of appropriately confirming efficacy and safety, to reliably conduct the evaluation within the approved time limit, and to aim for full approval.

2.6 Procedures after Conditional and Time-Limited Approval

The procedures after conditional and time-limited approval are explained below.

1. **Periodic reports on use-results surveillance and related information.** During the approved period of conditional and time-limited approval, periodic reports on use results and related information must be submitted within two months of the end of each reporting period, at intervals not exceeding one year (or such period as instructed by the Minister of Health, Labour and Welfare for specified regenerative medical products) calculated from the date designated by the Minister at the time of marketing authorization, pursuant to Article 23-26, paragraph 3 of the Act. For details, refer to the notification entitled "Partial Revision of the Notification on the Handling of Surveys of Use Results and Reexamination of Regenerative Medical Products" (MHLW PSB/MDED Notification No. 0424-4 and PSB/PSD Notification No. 0424-4, dated April 24, 2026).
2. **Changes to the post-marketing approval-condition evaluation plan.** If the evaluation plan is to be changed in light of post-marketing trends in adverse events or malfunctions, changes in treatment practices for the target disease, accumulation of post-marketing data, or other factors, PMDA should be consulted in advance.
3. **Handling of data collected after marketing.** It is desirable to consider sufficiently the handling, collection plan, and potential future use of data collected after marketing so that such data may also contribute to future development and approval applications for other regenerative medical products.
4. **All-case surveillance after completion of enrollment in the post-marketing approval-condition evaluation.** In principle, products subject to the Scheme will undergo post-marketing approval-condition evaluation covering all patients who use the product. Even after enrollment of cases subject to that evaluation has been

completed, use-results surveys or similar activities should be conducted for all patients using the product until disposition is made on the further approval application (1-2 application), so that the data can be submitted after the application. The plan for such surveys should also be discussed with PMDA at the time of the initial approval application (1-1 application), and the data cutoff should be discussed with PMDA before the further approval application (1-2 application) (see Figure 2).

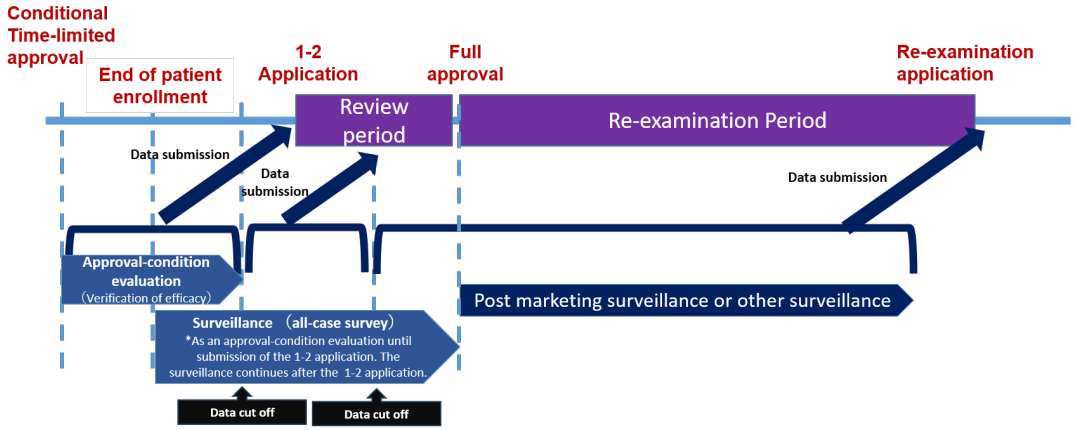


Figure 2. All-case surveillance continuing after the 1-2 application (Example)

5. **Extension of the approval period.** Under the Act, where particularly necessary for proper review, the approval period may be extended for a period not exceeding three years after hearing the opinion of the Pharmaceutical Affairs Council. The need for extension should be discussed with PMDA no later than 6 months before expiry.
6. **Partial changes to approved matters.** Pursuant to Article 23-25, paragraph 13 of the Act, as applied mutatis mutandis under Article 23-26, paragraph 4 of the Act, any person intending to make a partial change to the approved matters concerning the product is required to obtain approval for such change from the Minister of Health, Labour and Welfare, as in the case of regenerative medical products with full approval. However, for regenerative medical products with conditional and time-limited approval, applications such as addition of indications should be evaluated separately from the post-marketing approval-condition evaluation under the prior approval, and a new 1-1 Application should be required. PMDA should be consulted before submission regarding whether such a 1-1 Application is necessary.

2.7 Procedures for the Full Approval Application After Conditional and Time-Limited Approval

A marketing authorization holder of conditional and time-limited approval must submit a

further approval application (1-2 application) within the approved time limit. Before submitting that 1-2 application, if the sponsor wishes to consult on the organization of application materials or whether the data collected as post-marketing approval-condition evaluation verify efficacy for the target disease and further confirm safety, PMDA's consultation at the completion of post-approval clinical trials or other evaluations following conditional and time-limited approval should be used.

For the further approval application (1-2 application), a draft basic plan for post-marketing surveillance should be attached as part of the materials concerning risk analysis. After submission, PMDA reviews the application and prepares a review report, and the Pharmaceutical Affairs Council deliberates whether approval should be granted. If full approval is considered appropriate, the result is notified to prefectural governments and the Minister of Health, Labour and Welfare issues the approval notification to the applicant. At that point, the conditional and time-limited approval ceases to be effective, and full approval is newly granted. Even if the time limit for conditional and time-limited approval arrives after submission of the further application, the conditional and time-limited approval remains effective until disposition is made on that application.

If the Council concludes that full approval should not be granted, the result is notified to prefectural governments, and a non-approval notification is issued by the Minister of Health, Labour and Welfare to the applicant. If the time limit for conditional and time-limited approval has already expired before issuance of the non-approval notification, the conditional and time-limited approval ceases to be effective upon issuance of that notification. If the time limit falls after the date of issuance of the non-approval notification, the conditional and time-limited approval remains effective until the date of expiry. Accordingly, if the term of the conditional and time-limited approval has not yet expired as of the date on which the Pharmaceutical Affairs Council of the Ministry of Health, Labour and Welfare meets to deliberate whether full approval should be granted, and the Council concludes that full approval should not be granted, it will then proceed to deliberate whether the conditional and time-limited approval should be continued.

Because a product whose efficacy has not yet been fully verified is administered to patients at the stage of conditional and time-limited approval, the marketing authorization holder is expected to respect to the greatest extent possible the intentions and dignity of the medical institutions using the product and the patients receiving it. It is therefore extremely important to verify efficacy through post-marketing approval-condition evaluation and to make the results publicly available. Accordingly, even where full approval is granted, or where the marketing authorization holder submits a withdrawal of the further application or a notification

of cancellation of approval, the study results collected within the approval period are reviewed by PMDA, compiled into a review report, and made public.

After full approval is granted, use-results surveys or other post-marketing surveillance activities toward re-examination must be conducted. It should also be noted that patients treated with the regenerative medical product after submission of the further approval application (1-2 application) should be included in such surveillance, and data that could not be submitted during the further approval review must be submitted at the time of the re-examination application.

3. Review of the Results of Post-marketing Approval-Condition Evaluation and Regulatory Conclusions

As shown in Table 1, a total of eight regenerative medical products had received conditional and time-limited approval as of September 2026. Of these, two products, HeartSheet and Collategene Intramuscular Injection 4 mg, subsequently underwent a 1-2 application, for which regulatory conclusions have since been reached.

Reviewing the regulatory history and outcomes of these products provides important case examples for understanding the overall approval process designed to facilitate the early practical use of regenerative medical products and for ensuring the appropriate implementation of the approval scheme.

3.1 Results of HeartSheet

HeartSheet (hereinafter referred to as the “Product”) is a regenerative medical product consisting of autologous skeletal myoblast-derived cell sheets intended for the treatment of patients with severe heart failure associated with ischemic heart disease. In September 2015, the Product became the first regenerative medical product to receive conditional and time-limited approval under the Scheme newly introduced pursuant to the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (Act No. 84 of 2013), which came into effect in November 2014 (hereinafter referred to as the “amended PMD Act”).

The clinical evidence supporting this approval was derived from an exploratory study in which the Product was transplanted into seven patients with severe heart failure caused by ischemic heart disease. No serious safety concerns were identified. At Week 26, left ventricular ejection fraction (LVEF) had improved by approximately 7% on average, and improvement in New York Heart Association (NYHA) functional class was observed in the majority of patients. Improvement in exercise capacity, as measured by the six-minute walk distance, was also observed. Although these findings suggested the potential for

improvement in cardiac function, the data were exploratory, based on a small number of patients, and obtained without a control group. The efficacy of the Product was therefore considered to have been only “presumed,” and conditional and time-limited approval was granted.

The post-marketing approval conditions imposed on the Product required that its efficacy be verified in all treated patients and that its safety be further confirmed within the approval period by comparing the results of a use-results survey with those of a clinical study using an external control group.

During the conduct of the post-marketing evaluation, out-of-specification products, which had not occurred during the clinical trial, were identified, and considerable time was required to mitigate the risk of recurrence. In addition, the period between marketing approval and insurance coverage, including listing under the reimbursement price standard for medical materials, as well as the subsequent contracting process with institutions participating in the post-marketing approval-condition evaluation, took longer than anticipated. These factors made it difficult to enroll the target number of patients within the original approval period. Following deliberation by the Committee on Regenerative Medical Products and Biological Technology of the Pharmaceutical Affairs Council in November 2018, an extension of the approval period by three years, from the original five years to a total of eight years, was authorized in January 2019.

Approximately one year later, unforeseen circumstances arose, including severe pressure on healthcare services due to the spread of coronavirus disease 2019 (COVID-19). Nevertheless, in September 2023, based on the clinical data package obtained from the post-marketing approval-condition evaluation, an application for marketing approval of the Product following conditional and time-limited approval, as required under Article 23-26, paragraph 5 of the PMD Act, was submitted with the aim of obtaining full approval. This application is hereinafter referred to as the “1-2 application.”

The efficacy analysis population comprised 49 of the 67 patients enrolled in the Product group and 102 patients in the control group. Both groups consisted of patients with severe heart failure caused by ischemic heart disease who had an inadequate response to standard treatment. The primary endpoint was time to cardiac disease-related death, and efficacy was evaluated on the basis of survival outcomes. The secondary endpoints included: (i) time to hospitalization due to a major cardiovascular event; and (ii) the proportion of patients whose LVEF had improved by at least 5% at six months after transplantation.

Analysis using a propensity score-weighted Cox regression model yielded a hazard ratio of 1.9 for cardiac disease-related death in the Product group relative to the control group, with a 95% confidence interval (CI) of 0.8 to 4.4 and a two-sided p-value of 0.136. Thus, the

superiority of the Product over the control was not demonstrated for the primary endpoint. No clear difference was observed for the secondary endpoint of time to cardiac death or hospitalization due to a major cardiovascular event. With respect to improvement in LVEF, the proportion of patients achieving an improvement of at least 5% at 6 months was also not greater in the Product group than in the control group.

On the other hand, certain secondary endpoints yielded results suggestive of efficacy, including a trend toward improvement in NYHA functional class in the Product group and a trend toward a longer time to hospitalization requiring additional treatment for worsening heart failure. Based on an overall assessment of these findings, the applicant considered that the efficacy of the Product had been confirmed and consequently submitted the 1-2 application.

However, no statistically significant superiority was demonstrated in the larger real-world dataset, and the results were not consistent even across some of the endpoints that suggested efficacy. Accordingly, even after taking into account the inherent limitations of a study design involving comparison with an external control group, it was difficult to conclude that efficacy had been demonstrated. The evidence was therefore considered insufficient to support the benefit component of the benefit-risk balance.

With respect to safety, no new adverse events exceeding the risks identified at the time of conditional and time-limited approval were observed, and no increase in serious safety signals was identified. Ultimately, although the original determination at the time of conditional and time-limited approval that the Product's efficacy could be presumed was not itself rejected, the results of the post-marketing studies were considered not to have substantiated the efficacy of the Product.

At the meeting of the Committee on Regenerative Medical Products and Biological Technology of the Pharmaceutical Affairs Council held by the Ministry of Health, Labour and Welfare on July 19, 2024, it was concluded that approval of the Product would not be appropriate. This conclusion was subsequently endorsed by the Pharmaceutical Affairs Council at its meeting held on July 24, 2024. In response, the applicant submitted a notification of relinquishment of approval to the Pharmaceuticals and Medical Devices Agency (PMDA) and a notification of discontinuation of supply to the Ministry of Health, Labour and Welfare.

3.2 Results of Collategene Intramuscular Injection 4 mg

Collategene Intramuscular Injection 4 mg (the "Product") is a gene therapy regenerative medical product whose active ingredient is plasmid DNA expressing human hepatocyte growth factor, or HGF. In March 2019, it received conditional and time-limited approval for the improvement of ulcers in chronic arterial occlusive disease, namely arteriosclerosis

obliterans and Buerger's disease, in patients for whom standard pharmacological treatment was insufficient and revascularization was difficult.

At the time of approval, the review report concluded, based on the results of the ASO phase III study, the TAO general clinical study, and advanced medical care B clinical research, that a certain level of efficacy could be expected for ulcers in patients with critical limb ischemia due to chronic arterial occlusive disease for whom standard pharmacological treatment was insufficient and revascularization was difficult. At the same time, the efficacy information available at approval was limited, and it was assessed that the efficacy of the Product had not been verified.

Therefore, as a post-marketing approval-condition evaluation, during the period until the further approval application (1-2 application) after conditional and time-limited approval, a use-results comparative survey covering all patients treated with the Product was required in order to verify efficacy and collect safety information. In addition, because the Product is a gene therapy product and information on long-term prognosis was limited, it was considered appropriate to continue collecting information on safety, survival, and avoidance of lower-limb amputation from the second year onward until completion of the survey.

According to publicly available information, after conducting the approval-condition evaluation, the applicant submitted a marketing authorization application with the aim of transitioning the Product to full approval in May 2023, but subsequently announced withdrawal of the application and discontinuation of sales in June 2024. As a result, the Product did not transition to full approval after conditional and time-limited approval. In addition, at the meeting of the Pharmaceutical Affairs Council, Committee on Regenerative Medical Products and Biological Products, held on July 19, 2024, it was reported that the open-label use-results comparative survey did not reproduce the results of the domestic phase III clinical trial.

It should be noted that, in cases where an application was withdrawn, review reports were not previously made publicly available, as was the case with Collategene Intramuscular Injection 4 mg. Going forward, however, to ensure transparency in the conditional and time-limited approval scheme, the study results collected by the marketing authorization holder within the specified approval period will be reviewed by the PMDA, compiled into a review report, and made publicly available. For details, refer to the "Handling of Conditional and Time-Limited Approval for Regenerative Medical Products" (PSB/MDED Notification No.1006-1), dated October 6, 2025.

4. Considerations and Implications for Development Strategies for Regenerative Medical Products

The conditional and time-limited approval scheme has been operated as a framework that supports the early practical application of regenerative medical products and facilitates early patient access to such products. This fundamental principle remains unchanged even now, more than ten years after the implementation of the scheme. From a regulatory review perspective, the most significant differences between this scheme and the ordinary approval pathway are that approval is granted on the basis that efficacy is presumed and safety is confirmed, and that the subsequent verification of efficacy and further confirmation of safety are imposed as conditions of approval. Verification of efficacy inherently involves testing a prespecified hypothesis, and achievement of the primary endpoint is therefore a fundamental principle. This section sets out FIRM's views on key considerations and implications for the future development of regenerative medical products. Because the presumption of efficacy may be based on an evaluation involving an extremely limited number of patients, the use of surrogate endpoints may be acceptable. However, when verifying efficacy through the post-marketing approval-condition evaluation, it is important to assess not only the efficacy of the product itself but also the clinical utility of the treatment as a whole. For example, where treatment involves a surgical procedure, the clinical utility of the entire treatment, including the surgical procedure, should be verified. It should also be recognized that, because such verification is conducted through use-results surveys or similar post-marketing investigations, the types and amounts of data that can be collected may be limited. Given the various uncertainties that may arise, the study design should be considered with particular care before initiation. This includes designing endpoints that enable rigorous evaluation even with a small number of patients and introducing novel statistical analysis methods, where appropriate. Consultation with PMDA is also advisable. Time-related factors are also important considerations under this scheme. Depending on the study design, prolonged patient enrollment may create a temporal difference between the treatment and control groups. If the standard of care changes during this period, for example, as a result of the introduction of an innovative new therapy, the interpretation of the final study results may be substantially affected. In all cases, it should be kept in mind that this scheme does not represent the endpoint of product development. Rather, it forms part of an ongoing development process through which confirmatory evidence continues to be collected in the post-marketing setting. Based on the above, FIRM considers that the following elements should be incorporated into development strategies for regenerative medical products:

- **Early planning based on the need for post-marketing evidence:**
  A development plan that incorporates the ultimate demonstration of efficacy using post-marketing data should be established from an early stage of development.
- **Selection of scientifically valid endpoints appropriate to the product**

characteristics:

In view of the possibility that evaluation may have to be conducted in a small number of patients, consideration should be given to the use of surrogate or composite endpoints and to whether the selected endpoints can support verification of efficacy.

- **Validity and robustness of the clinical study design:**

  When an external control group or an open-label study design is used, the validity of between-group comparisons and the effects of potential sources of bias should be rigorously assessed.

- **Establishment of statistical superiority over conventional treatment:**

  For the benefit-risk assessment, clear clinical utility over the existing standard of care should be statistically demonstrated, rather than relying on results that merely suggest efficacy.

- **Control of temporal bias and management of data quality:**

  Strategies should be established to facilitate rapid patient enrollment based on a realistic assessment of feasibility and to minimize temporal bias.

- **Securing sufficient time for reimbursement procedures and agreements with medical institutions:**

  In setting and proposing to the regulatory authorities the desired period of conditional and time-limited approval, the applicant should take into account the time required for reimbursement procedures and for negotiating agreements with medical institutions participating in use-results surveys and other post-marketing investigations.

To increase the likelihood of successful development of regenerative medical products, it is essential to establish, from an early stage of development, a development framework that closely integrates scientific rationale with regulatory and operational requirements.

5. Issues in Conducting Post-Marketing Approval-Condition Evaluation

This chapter summarizes practical issues and points to consider in conducting post-marketing approval-condition evaluation under conditional and time-limited approval, based on the purpose of the Scheme, relevant notifications and procedures, and case examples discussed in the preceding chapters. The aim is to support marketing authorization holders in considering development plans and evaluation plans.

The matters discussed in this chapter mainly represent examples of insights obtained from practical experience with use-results comparative surveys. Accordingly, the issues and approaches described here do not necessarily apply uniformly to all regenerative medical products. At the same time, organizing the general concepts set out in notifications and guidance in relation to practical issues that may arise in implementation may be useful when considering evaluation plans.

For individual products, it is important to develop evaluation plans from the perspectives of both feasibility and scientific validity, taking into account the product characteristics, disease characteristics, and evaluation approach, and using regulatory consultations where appropriate.

5.1 Points to Consider When Designing the Survey

5.1.1 Estimation of the Number of Patients and Sites, and Process Design

In post-marketing approval-condition evaluation, data necessary to verify efficacy and confirm safety must be collected and analyzed within the approval period and linked to the further approval application (1-2 application). Accordingly, when considering the number of cases and evaluation sites, it is desirable to take into account not only scientific and statistical validity, but also feasibility, including the execution of survey contracts with medical institutions, the establishment of survey implementation schemes within each site, and the time required for site initiation, as well as estimated case enrollment.

As discussed later, depending on various factors, it may take more than one year before a site is actually able to administer the product. In light of this possibility, it is useful to organize in advance the prioritization of candidate sites and the concept of parallel site start-up.

5.1.2 Objectivity and Standardization of Evaluation

Because the post-marketing approval-condition evaluation is required to verify efficacy, greater emphasis is placed on the objectivity of the data collected after approval and the validity of the evaluation. Where blinded evaluation is difficult, standardization of evaluation methods and third-party assessment, such as central review, may be important measures to reduce bias.

Endpoints should be selected, to the extent possible, so that they are objective and quantitative and are relatively less affected by evaluator subjectivity or site-to-site variability. In some disease areas, however, established indicators may be limited, or certain subjective elements may be unavoidable due to the nature of the evaluation method. Even in such cases, the validity of the evaluation can be enhanced by combining measures to reduce bias, such as clarifying evaluation procedures and decision criteria and providing training to evaluators. Where a third-party committee or central review committee is established, it is desirable to define before the start of evaluation the committee membership, adjudication procedures, operating rules, format of materials for review, data storage, and audit readiness. When electronic records such as videos or images are used for third-party evaluation, attention should be paid to practical implementation issues, including masking of personal information and information that may identify treatment groups, requirements for camera angle, duration, and audio, and the physical environment at the site, such as space and

background noise. Rather than requiring sites to implement an idealized plan as written, it is important to translate the plan into standard procedures that can be implemented in actual clinical settings.

In addition, where evaluation items not performed in routine clinical practice are included, or where electronic records such as videos are required, the burden on physicians and staff at medical institutions may increase, and securing an implementation scheme may become an issue. At the planning stage, it is useful to organize the rationale for requiring such evaluations, the degree of burden on patients and medical institutions, and the intended use of the data, and to prepare materials that will support understanding by medical institutions.

5.1.3 Setting of the Control Group

When a control group is established in a use-results comparative survey or similar framework, how the control group data are obtained and the extent to which comparability can be ensured are critical to conducting a scientifically valid evaluation.

The method for obtaining control-group data and the extent to which comparability can be ensured affect the persuasiveness of the evaluation. The nature of potential bias differs depending on whether data are collected prospectively during the same period or whether historical data, registry data, or other retrospective data are used.

When retrospective data are used, it is necessary to confirm in advance whether the necessary endpoints are available and whether assumptions for comparison are valid, including whether differences in region or timing of data collection may affect patient background or treatment patterns.

Even where data are collected prospectively, if patient backgrounds differ between the product group and the control group, it is difficult to regard the two groups as sufficiently comparable. In comparisons that do not involve randomization or blinding, potential sources of bias that could affect the evaluation, including patient selection bias during the patient enrollment process, should be considered, and appropriate measures to avoid or minimize such bias to the extent possible should be incorporated into the evaluation plan. Therefore, when establishing a control group, it is important, regardless of how the control group data are obtained, to carefully consider, from the planning stage, factors that may affect comparability and measures to address them, so as to enable a scientifically valid evaluation.

5.2 Issues That May Arise in Coordination with Medical Institutions and Establishment of Implementation Schemes

5.2.1 Explaining the Positioning of Approval-Condition Evaluation and the Setting of a Control Group

Conditional and time-limited approval is a scheme that enables early patient access to

regenerative medical products whose efficacy has been presumed at an early stage of clinical development. In approval-condition evaluation, data necessary to verify efficacy and further confirm safety must be collected and organized within the limited post-approval period. However, even where the name and purpose of the Scheme are recognized at medical institutions, the positioning of approval-condition evaluation may not always be sufficiently shared among stakeholders.

In particular, when a control group is established in a use-results comparative survey, the comparison involves a population that does not receive the product even though access to the regenerative medical product granted conditional and time-limited approval has become available to a certain extent. In such situations, medical institutions may question the regulatory or ethical positioning of establishing a group that does not receive the product as the comparator.

Such issues are more likely to become apparent where the purpose of the Scheme and the concept of approval-condition evaluation have not been sufficiently shared. Although it is difficult to provide a uniform solution, it is desirable to explain carefully to medical institutions the background to setting the control group and the positioning of the overall evaluation plan, and to ensure consistency among the materials presented and the explanations provided.

5.2.2 Addressing Differences in Institutional Procedures and Practices and Site Initiation

Even when the marketing authorization holder presents the same evaluation plan and provides the same explanation to each medical institution, the manner in which the evaluation is handled internally and the institutional procedures required may vary depending on the rules and practices of each institution. Consequently, the matters to be confirmed and the progress of the required procedures may differ among institutions, and a considerable amount of time may be required before the evaluation can be initiated.

It should also be noted that delays in site initiation may affect the feasibility of implementing the evaluation plan as a whole. In view of differences in practices among medical institutions, it is advisable to identify and prepare the necessary documents and explanatory materials at an early stage and to ensure sufficient flexibility to respond to the circumstances of each institution.

5.3 Major Risks Anticipated During Implementation

5.3.1 Securing Support Structure and Risk of Delayed Data Collection

In approval-condition evaluation, the burden on medical institutions may be substantial because there may be many evaluation items, detailed evaluation time points, and complex data entry requirements. In general, under post-marketing surveillance and similar

frameworks, some institutions may not have the same level of clinical research coordinator (CRC) placement or site management organization (SMO) support as in clinical trials. As a result, institutional rules may make it difficult or impossible to assign coordinators for surveys, causing practical workload to concentrate on physicians and staff and thereby contributing to delayed data collection.

From the perspective of reducing physician burden and ensuring data quality, it is desirable to consult early with medical institutions regarding the support schemes that may be required on their side. Even where coordinator placement is difficult under institutional operations because the activity is treated as a survey, considering forms of support that are permissible within the institution may help reduce the risk of delayed data collection.

In disease areas with low case frequency, procedures and completion instructions may be forgotten by the time the next case is handled, and repeated explanations may be necessary. Education and training should therefore not be treated as a one-time activity; rather, a continuing support scheme should be established with attention to retention and practical implementation.

5.3.2 Ensuring Data Quality

In use-results comparative surveys and similar activities conducted under the GPSP framework, it is difficult to apply the same operational approach as source data verification commonly conducted in clinical trials for all cases and all items. In practice, methods for ensuring reliability must be designed and implemented while taking into account institutional operations, access rights, and the handling of personal information.

In collecting survey forms, an increase in follow-up inquiries or queries may create a burden for both medical institutions and sponsors. Therefore, it is useful to reduce errors at the time of entry by clarifying input rules, providing examples, and establishing entry check points in advance. For example, when electronic data capture (EDC) is used, it is important to design EDC to be user-friendly from the development stage.

5.3.3 Patient Follow-Up and Continuous Information Collection Schemes

Depending on the target disease and treatment process, patient follow-up may span multiple medical institutions due to transfer or other changes in care setting. In such cases, ensuring continuity of data when the patient’s outpatient or inpatient care site changes may become an issue.

Where this is anticipated, it is important to define in advance which institution is responsible for information at each time point and by what procedure information will be transferred.

5.4 Issues Relating to Switching or Transitioning Surveys

5.4.1 Setting the Data Cut-Off

In approval-condition evaluation, a data cut-off date must be set because data analysis will be conducted for use in the further approval application (1-2 application). The data cut-off is an important issue from the perspective of transparency because it constitutes a premise for the analysis. If the cut-off is set retrospectively, it may be perceived as arbitrary. Therefore, taking into account the observation period of patients and other relevant factors, it is desirable to define the anticipated timing as clearly as possible at the planning stage and, where necessary, to set it in consultation with PMDA.

5.4.2 Decision-Making Timeline for Plan Changes and Extension of the Approval Period

As a general principle, a post-marketing approval-condition evaluation requires the enrollment of the necessary number of patients and the collection of the data required for the evaluation within the specified approval period. However, where an extension is deemed particularly necessary to ensure an appropriate regulatory review, the period of conditional and time-limited approval may be extended by up to three years after consultation with the Pharmaceutical Affairs Council. The need for such an extension must be discussed with the PMDA no later than six months before the expiration of the approval period.

Accordingly, it is important to establish a management scheme that enables the early identification of indications that may affect the progress of the post-marketing approval-condition evaluation, such as delays in patient enrollment or missing data, and to consult with PMDA as necessary.

5.4.3 Considerations for the Transition from the Approval-Condition Evaluation to Post-marketing Surveillance for Re-examination

Once a renewed approval application following conditional and time-limited approval, referred to as a “1-2 application,” has been submitted, the Product may continue to be supplied until a regulatory decision is made on the application. If approval is subsequently granted, post-marketing surveillance and other activities required for re-examination must be conducted.

Accordingly, approval-condition evaluation conducted under conditional and time-limited approval and the subsequent post-marketing surveillance or other activities toward re-examination may be handled continuously in practice, and the handling of surveys and cases may become an issue. Although the applicable notification sets out the basic regulatory requirements, practical coordination may be necessary with respect to matters such as contracts with participating institutions and internal institutional procedures. Explaining the

transition to medical institutions and obtaining their understanding may also present practical challenges.
In addition, when switching or transitioning surveys, new contracts with medical institutions or IRB review may be required. Therefore, it is desirable to organize the handling of cases and surveys from an early stage while making use of consultation with PMDA.

5.5 Section Summary

The issues presented in this chapter are based primarily on practical experience with use-results comparative surveys and are not intended to comprehensively cover all issues that may arise in approval-condition evaluation conducted under conditional and time-limited approval for diverse regenerative medical products.
Nevertheless, issues such as ensuring objectivity and scientific validity of evaluation, setting a control group, site start-up, data quality, and switching or transitioning surveys may require attention when considering evaluation plans regardless of the product.
In light of the above, marketing authorization holders should take into account the purpose of the scheme and practical constraints and assess the feasibility of implementing the evaluation plan in specific terms from an early stage. It is also important to develop scientifically valid and highly feasible development and evaluation plans, making use of consultations with the regulatory authorities and other available mechanisms, as appropriate.

Conclusion

The Scheme was established in consideration of the characteristics of regenerative medical products. Under the Scheme, conditional and time-limited approval may be granted at a stage when a certain level of efficacy is presumed and safety has been confirmed. The Scheme is premised on the subsequent verification of efficacy and further confirmation of safety through post-marketing approval-condition evaluation, followed by transition to full approval.

The Scheme not only enables early patient access to innovative therapies but also facilitates seamless development encompassing the entire process from the pre-marketing presumption of efficacy through post-marketing safety measures. It is therefore expected to clarify the development process, increase the likelihood of successful development, and enhance business predictability, thereby providing value to sponsors. Accordingly, the Scheme should not be regarded merely as a scheme for deferring the verification of efficacy or as one intended solely to provide early patient access.

As illustrated by the cases of HeartSheet and Collategene Intramuscular Injection 4 mg, even where efficacy is expected at the time of conditional and time-limited approval, a product will not obtain full approval, and its conditional and time-limited approval may ultimately cease to be effective, unless its efficacy can be verified in a scientifically valid manner through post-marketing approval-condition evaluation. Therefore, when considering use of the Scheme, it is important to comprehensively assess, from an early stage of development, the endpoints, control group, objectivity of the evaluation, patient enrollment, data quality, collaboration with medical institutions, and the feasibility of completing the required evaluation within the specified approval period, and to establish a consistent development plan with a view to ultimately obtaining full approval.

To this end, sponsors seeking to use the Scheme must correctly understand the relevant notifications and guidance, PMDA consultations, and post-approval procedures. From the time of submission of the Category 1-1 marketing authorization application, or “1-1 application,” it is essential to carefully assess feasibility and establish a detailed plan for generating scientifically valid evidence through post-marketing approval-condition evaluation sufficient to support full approval.

Finally, we would like to reiterate the importance of respecting the dignity of patients who place their hopes on gaining early access to treatment through the Scheme and ensuring that obtaining conditional and time-limited approval does not become an end in itself. It is our sincere hope that this Guide will assist sponsors in developing strategies that increase the likelihood of ultimately obtaining full approval.

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