

PSEHB/MDED Notification No. 0729-1

July 29, 2021

To: Director-General of the Prefectural Health Department (Bureau)

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

Handling of Applications for Confirmation of Change Management Protocol of  
Regenerative Medical Products

The Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (Act No. 145 of 1960, hereinafter referred to as the “Act”) has been partially amended by the Act Partially Amending the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (Act No. 63 of 2019) promulgated on December 4, 2019. A part of the amended content will be enforced on August 1, 2021.

The currently established post-approval change management protocol (PACMP) for confirmation of a change management protocol of regenerative medical products and changes made according to the protocol will be handled as provided below. Please understand this notification and ensure that organizations and institutions concerned under your jurisdiction are thoroughly informed. This notification shall apply starting on August 1, 2021.

\*\*\*

Section 1 Scope of this notification

To make changes to regenerative medical products approved under Article 23-25, Paragraph 1 of the Act, the following procedure is required: (a) a person who intends to formulate a change management protocol of the regenerative medical products concerned under provisions of Article 23-32-2 of the Act (including cases applied mutatis mutandis under Article 23-39 of the Act with modifications, hereinafter the same) and to implement it, or have a designated marketing authorization holder implement it, submits an application for confirmation of change management protocol; and (b) the confirmation of the change management protocol is performed as appropriate. The scope of the change management protocol of regenerative medical products includes shape, structure, ingredients, quantities or nature (except for constitutive cells or transgenes), manufacturing method, storage method and shelf life, specifications and testing methods, and manufacturing sites of products to be marketed.

This notification shall apply to products included in applications for confirmation of change management protocol of regenerative medical products under provisions in Article 23-32-2 of the Act. A change management protocol that is subject to the application for confirmation should be formulated to be ethical, scientific, and reliable based on the academic standards of medicine, pharmacy, engineering, etc. at the time of formulation and to provide adequate data that support the demonstration or estimation of post-change quality, efficacy, and safety of regenerative medical products included in an application for confirmation.

For the time being, any person who wishes to have a change management protocol confirmed should apply to the Pharmaceuticals and Medical Devices Agency (hereinafter referred to as “PMDA”) for a consultation to seek advice on whether the change management protocol to be submitted is subject to this notification.

- 1 Changes in approved items eligible for confirmation of a change management protocol should meet the following conditions.
  - (1) Changes to items provided in Article 137-48-3 of the Regulation for Enforcement of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (Ministry of Health and Welfare Ordinance No. 1 of 1961, hereinafter referred to as the “Regulation”) amended by the Ministerial Ordinance on the Development of Related Ministerial Ordinances in Accordance with Enforcement of the Act Partially Amending the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (MHLW Ordinance No. 15 of 2021)
  - (2) Changes that are not defined in Article 137-48-4 of the Regulation and for which a change management protocol includes regenerative medical products not defined in Article 137-48-5 of the Regulation
- 2 For the time being, changes to the content registered in drug master files are not eligible.

Section 2 Information to be filled in application forms for confirmation of a change management protocol of regenerative medical products

- 1 Information to be filled in application forms for confirmation of a change management protocol of regenerative medical products

An application form for confirmation of a change management protocol should be filled with information defined as matters to be filled in application forms for confirmation of a change management protocol of regenerative medical products in Article 137-48-2, Paragraph 1 of the Regulation as well as approval number and date of approval for the approved products or system receipt number and date of approval application for ones under approval application. In addition, the “Remarks” field in an application form for confirmation of a change management protocol of regenerative medical products should be given the following information: (a) number of face-to-face

consultation where applicable; (b) name of data to be attached to the application form (hereinafter referred to as the “attached data”) listed in Article 137-48-2, Paragraph 3 of the Regulation; and (c) history of changes in approved items made after the first approval. The application form for confirmation of a change management protocol of regenerative medical products must be completed in Japanese.

## 2 Handling of data to be attached and points to note for preparation

(1) The attached data must be collected and prepared under provisions in Article 137-25 of the Regulation.

(2) The attached data should include the following documents. In principle, the attached data should be submitted as electronic files in PDF format or other formats prepared by converting original electronic data. If the electronic data are not available, files in PDF format prepared by scanning and converting original copies of the documents concerned should be submitted.

1) Draft corrected application form for approval reflecting the change management protocol and table for comparison between relevant texts before and after the changes (including a draft table for comparison between new and old application forms for approval) (relating to Article 137-48-2, Paragraph 3, Item 1, a of the Regulation)

2) Change management protocol

The change management protocol should include the following documents.

- Changes and their detailed descriptions including justification (relating to Article 137-48-2, Paragraph 3, Item 1, a of the Regulation)
- List of studies or investigations to evaluate potential impacts of changes on quality as well as their testing methods and acceptance criteria, prepared based on risk assessment (including characterization, release tests, stability studies, and in-process control tests) (relating to Article 137-48-2, Paragraph 3, Item 1, b of the Regulation)
- Compliance with the approved control strategy or discussion about changes of the control strategy required in response to the intended changes (relating to Article 137-48-2, Paragraph 3, Item 1, c of the Regulation)
- Other conditions that should be met (relating to Article 137-48-2, Paragraph 3, Item 1, d of the Regulation)
- Where applicable, reference data useful in minimizing risks, obtained from prior experiences with the same or similar products, covering development, manufacture, characterization, release tests, and stability studies (relating to Article 137-48-2, Paragraph 3, Item 1, d of the Regulation)
- Draft package insert if its revision is expected (relating to Article 137-48-2, Paragraph 3, Item 1, d of the Regulation)

- Necessity of application for confirmation of compliance status of regenerative medical products (relating to Article 137-48-2, Paragraph 3, Item 1, a of the Regulation)
- 3) Prior approvals for partial changes in approved items under provisions in Article 23-25, Paragraph 11 of the Act or history of approvals after the first approval if minor change notifications have been submitted under provisions in Article 137-29 of the Regulation. Duplicate copies of approval certificates for the products concerned and duplicate copies of minor change notifications submitted during a period from the approval for the products concerned or the last approval of partial changes in approved items to the application for confirmation of a change management protocol (relating to Article 137-48-2, Paragraph 3, Item 1, d of the Regulation)
- (3) If an application form for confirmation of a change management protocol is submitted in a format of Common Technical Document (hereinafter referred to as “CTD”), the attached data including the change management protocol should be stored in a flexible disk (hereinafter referred to as “FD”) for application form as a change management protocol file as well as in Module 2.3.R and Module 3. If the CTD format is not used for submission of an application form for confirmation of a change management protocol, the attached data including the change management protocol should be stored in the FD for application form as a change management protocol file as well as in Section 2, Appended Tables 1-2 and -3 in the “Applications for Marketing Approval of Regenerative Medical Products” (PFSB Notification No. 0812-30, dated August 12, 2014, of the Pharmaceutical and Food Safety Bureau of the Ministry of Health, Labour and Welfare [MHLW]). Documents to be stored in the FD for application form as well as in Module 2.3.R or Appended Tables 1-2 and -3 of the concerned notification should be prepared in Japanese.
  - (4) Data to be attached to the application form for confirmation of a change management protocol of regenerative medical products should be prepared in Japanese in principle. If the concerned attached data are prepared in English, they may be directly submitted, but the summary prepared in Japanese should be additionally submitted in principle.

### Section 3 Handling when a change management protocol is changed

- (1) To change a confirmed change management protocol, the following actions can be taken as specified in Article 137-48-2, Paragraph 2 of the Regulation: (a) for minor changes, notifications defined in Article 137-48-7, Paragraph 1 of the Regulation may be submitted; and (b) for non-minor changes, applications for confirmation should be made under the second sentence of Article 23-32-2, Paragraph 1 of the Act. Concerning whether a change is applicable to any of the items listed in Article 137-48-7, Paragraph 2 of the Regulation, consultation with PMDA should be made where necessary.

(2) For applications for confirmation of changes to the confirmed change management protocol, the “Remarks” field in the application form for confirmation defined in Article 137-48-2, Paragraph 2 of the Regulation should include (a) details of the changes to the confirmed change management protocol; and (b) history of changes after the first confirmation of the change management protocol and reasons for the changes, if confirmation has been obtained in response to an application for confirmation submitted under provisions in the second sentence of Article 23-32-2, Paragraph 1 of the Act after the preceding confirmation of the change management protocol or if notifications have been submitted under Article 137-48-7, Paragraph 1 of the Regulation. The application form for confirmation should be prepared in accordance with Section 3.1. The attached data should include matters listed in Section 3.2 and information defined below. Parts of the change management protocol not subject to changes may be omitted from the attached data to be submitted, but absence of the changes in the concerned parts should be explained.

- 1) Changes from the agreed change management protocol, including secondary changes such as a change in necessity for confirmation of compliance status of the regenerative medical products, and justification for the changes (should be included in the draft change management protocol)
- 2) For changes subject to applications for confirmation under provisions in the second sentence of Article 23-32-2, Paragraph 1 of the Act, a draft corrected version of the application form for approval reflecting the change management protocol and table for comparison between relevant texts before and after the changes (including a draft table for comparison between new and old application forms for approval)
- 3) Duplicate copies of prior confirmation result notifications
- 4) Data on notifications submitted under provisions in Article 137-48-7, Paragraph 1 of the Regulation where applicable
- 5) Duplicate copies of all previously confirmed change management protocols

If a change management protocol has to be drastically changed, an application for confirmation of a new change management protocol may be separately required instead of the application for confirmation of changes to the confirmed change management protocol. Consultation with PMDA should be made where necessary.

(3) If a minor change notification for the confirmed change management protocol is submitted, the draft post-change change management protocol to be attached to the notification form defined in Article 137-48-7, Paragraph 1 of the Regulation should include changes from the agreed change management protocol and justification for the changes. In addition, a draft application form for approval that reflects changes defined in the change management protocol and table for

comparison between relevant texts before and after the changes (including a draft table for comparison between new and old application forms for approval) should be attached.

- (4) The confirmation certificate will be issued when confirmation of changes in a change management protocol is completed.

#### Section 4 Handling of changes made according to a change management protocol

##### 1 Compilation method of notification form for changes made according to a change management protocol

- (1) Data to be attached to a notification form for changes made according to a change management protocol defined in Article 137-48-13, Paragraph 2 of the Regulation should include the following documents. In principle, the data to be attached should be submitted as electronic files in PDF format or other formats prepared by converting original electronic data. If the electronic data are not available, files in PDF format prepared by scanning and converting original copies of the documents concerned should be submitted. The data should be prepared based on information obtained according to the confirmed change management protocol. In addition, a written statement should be submitted that the concerned data have been collected and prepared under provisions in Article 137-25 of the Regulation.

- 1) Study results demonstrated to meet predetermined acceptance criteria and overview
- 2) Duplicate copies of confirmation result notifications for compliance status of regenerative medical products if the confirmation of compliance status is required.
- 3) Relevant texts in a draft corrected application form for approval reflecting the change management protocol and a table for comparison between them before and after the changes (including a draft table for comparison between new and old approval certificates)
- 4) Duplicate copies of prior confirmation result notifications
- 5) Data on notifications submitted under provisions in Article 137-48-7, Paragraph 1 of the Regulation where applicable
- 6) Current change management protocol
- 7) Duplicate copies of approval certificates (including those of prior approval certificates for partial changes in approved items where applicable)
- 8) Duplicate copies of minor change notifications submitted during a period from approval for the products concerned, previous partial change approval, or previous confirmation of the change management protocol to submission of notification for changes made according to the change management protocol

##### 2 Handling after notification for changes made according to a change management protocol

- (1) Changes made according to a change management protocol are usually allowed after 40 working days at PMDA have passed since acceptance of the notification concerned. However, in the

following case, such changes are allowed after 20 working days at PMDA have passed since acceptance of the notification: 1) no minor change notifications have been submitted since the most recent approval for matters eligible for applications for confirmation of a change management protocol (matters listed in Article 137-48-3 of the Regulation); and 2) no notifications defined in Article 137-48-7 of the Regulation have been submitted since the last confirmation of the change management protocol.

(2) In the following cases, changes made according to a change management protocol are not allowed, and appropriate actions such as cancellation of changes related to the notification are required to be taken if instructed by the Minister of Health, Labour and Welfare under provisions in Article 23-32-2, Paragraph 7 of the Act. In addition, if changes deemed to be inconsistent with a change management protocol are to be made, an application for approval of partial changes in approved items for marketing will be required for the changes concerned.

- 1) Where changes according to a confirmed change management protocol have not been made;
- 2) Where study results are not obtained as expected in a confirmed change management protocol; and
- 3) Where changes in a confirmed change management protocol have been made, and it is revealed that they have been addressed by notifications defined in Article 137-48-7 of the Regulation, although they should have been essentially addressed by applications defined in Article 23-32-2, Paragraph 1 of the Act in view of the extent of the changes.

In the cases in 2) above, the marketing authorization holder, etc. should examine whether the change management protocol itself needs to be reviewed, and consultation with PMDA should be made where necessary. If whether any of 1) to 3) above is applicable remains unknown, for example, study results obtained under the confirmed change management protocol raise a doubt, the Ministry of Health, Labour and Welfare and PMDA may check the applicability.