Administrative Notice
December 22, 2021

To: Pharmaceutical Affairs Section, Prefectural Health Department (Bureau)

Medical Device Evaluation Division,
Pharmaceutical Safety and Environmental Health Bureau,
Ministry of Health, Labour and Welfare

Questions and Answers (Q&A) on Applications for Confirmation of Change Management Protocol of Regenerative Medical Products

Handling related to applications for confirmation of change management protocol of regenerative medical products has been presented in the "Handling of Applications for Confirmation of Change Management Protocol of Regenerative Medical Products" (PSEHB/MDED Notification No. 0729-1, dated July 29, 2021, of the Medical Device Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare [MHLW]).

As provided in the appendix, questions and answers (Q&A) for handling applications for confirmation of a change management protocol such as a method of submission and data compilation have been organized. Please ensure that relevant companies under your jurisdiction are thoroughly informed of them.

Appendix

Questions and Answers (Q&A) on Applications for Confirmation of Change Management Protocol of Regenerative Medical Products

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[Abbreviations]
Act: The Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (Act No. 145 of 1960)

Enforcement Regulation of the Act: 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)

PSEHB/MDED Notification: "Handling of Applications for Confirmation of Change Management Protocol of Regenerative Medical Products" (PSEHB/MDED Notification No. 0729-1, dated July 29, 2021, of the Medical Device Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, MHLW)

Application for approval: Application for approval of marketing under provisions in Article 23-25, Paragraph 1 of the Act

Application for approval of partial changes: Application for approval of partial changes in approved items under provisions in the first sentence of Article 23-25, Paragraph 11 of the Act

Application for approval, etc.: Application for approval of marketing or application for approval of partial changes in approved items for marketing

Application for confirmation of change management protocol: Application for confirmation under provisions in Article 23-32-2, Paragraph 1 of the Act

Application for confirmation of changes in change management protocol: Application for confirmation under provisions in the second sentence of Article 23-32-2, Paragraph 1 of the Act

Notification for changes in change management protocol: Notification under provisions in Article 23-32-2, Paragraph 6 of the Act

CTD: Common Technical Document

FD: Flexible disk

[Note]
This Q&A presents interpretations on the PSEHB/MDED Notification above, but if any doubt is raised concerning an application for confirmation of a change management protocol, irrespective of its applicability to this Q&A, consultation with the application address for review at the Pharmaceuticals and Medical Devices Agency (hereinafter referred to as "PMDA") should be considered.

1. General matters

Q1: Are regenerative medical products with conditional and time-limited approval eligible for applications for confirmation of a change management protocol?

A1: Yes

Q2: Section 1 of the PSEHB/MDED Notification has a phrase “ingredients, quantities or nature (except for constitutive cells or transgenes).” Are changes in specifications and testing methods on nature without constitutive cells or transgenes, shape, structure, ingredients, or quantities eligible?

A2: Because changes in constitutive cells or transgenes essentially determining the nature of a regenerative medical product are considered to have impacts on efficacy and safety of the final product, they are not eligible for applications for confirmation of a change management protocol (see Article 137-48-3 of the Enforcement Regulation of the Act). On the other hand, changes in specifications and testing methods on nature, shape, structure, ingredients, or quantities without constitutive cells or transgenes that are applicable to Article 23-32-2, Paragraph 1, Items 2 and 3 of the Act are eligible for applications for confirmation of a change management protocol.

Q3: To proceed with an application for confirmation of a change management protocol smoothly, how should we use consultation with PMDA?

A3: If you want to consult PMDA regarding the eligibility for an application for confirmation of a change management protocol and the schedule to proceed with such application in advance, you can ask PMDA to have a pre-consultation meeting. Regarding details in a change management protocol, you can ask PMDA to provide consultation on the quality of regenerative medical products.

Q4: For a product under application for approval, etc., can an application for confirmation of a change management protocol be submitted before the application concerned is approved?

A4: Yes

Q5: Does the regulatory process with an application for confirmation of a change management protocol for a product under application for approval take a similar period of time to that of the process for an approved product?

A5: If an application for confirmation of a change management protocol is submitted during the review for an application for approval, etc. of the product that is intended to have the change management protocol confirmed or simultaneously with an application for approval, etc. of such product, it should be noted that the change management protocol is not confirmed until the application for approval, etc. is approved, because the protocol cannot be agreed at a stage where the application for approval, etc. is not approved. An application for confirmation of changes in a confirmed change management protocol, if any, is handled in a similar manner.

2. Data to be submitted with application for confirmation of change management protocol

Q6: In the case where a change management protocol is planned at the time of an application for approval, etc., is simultaneous submission of an application for confirmation of the change management protocol allowed by storing attached data including the change management protocol in CTD Module 2.3.R and Module 3, as provided in Section 2.2 in the PSEHB/MDED Notification?

A6: An application for confirmation of a change management protocol can be submitted simultaneously with an application for approval. In this case, data submitted for the application for approval of the product for which the change management protocol is to be confirmed may include the attached data containing the change management protocol. However, if a change management protocol to be confirmed is included, CTD Module 2.3.R should have a statement that it is a draft at the time of an application for approval but not confirmed. Of note, if the application is submitted in non-CTD format, the above statement should be put in an appropriate place.

Q7: In the case where an application for confirmation is submitted in CTD format, where should documents defined in Section 2.2 (2) 1) to 3) of the PSEHB/MDED Notification be stored?

A7: The documents defined in Section 2.2 (2) 1) and 2) of the PSEHB/MDED Notification should be stored in CTD Module 2.3.R, with their duplicate copies included in CTD Module 1.2. Supporting data or reports, if any, should be stored in CTD Module 3.2.R, and references should be stored in CTD Module 3.3. The documents defined in Section 2.2 (2) 3) of the PSEHB/MDED Notification may be handled as done for an application for approval of partial changes. Of note, if the application is submitted in non-CTD format, these documents may be stored in an appropriate place with actions taken to clarify a storage place of each document.

Q8: Regarding duplicate copies of minor change notifications required in Section 2.2 (2) 3) of the PSEHB/MDED Notification, are duplicate copies only of notification forms involving the major items related to the change management protocol acceptable? In addition, may a draft application form for approval and a draft table for comparison between new and old application forms for approval, which are submitted simultaneously, reflect these minor change notifications?

A8: Duplicate copies of minor change notifications that have not been reviewed because of the prioritized review for the partial change approval should be included in the data attached to an application form for confirmation of a change management protocol. However, duplicate copies of notifications involving major items that are unrelated to the change management protocol are not required. In addition, related minor change notifications may be reflected in the draft application form for approval and the draft table for comparison between new and old application forms for approval, but the table should be designed to clearly identify the items subject to the notifications by underlining the relevant parts.

Q9: When the "Remarks" field in an application form for confirmation of a change management protocol is filled with a history of changes in approved items made after the first approval, what information should be filled?

A9: In the "Remarks" field in an application form for confirmation of a change management protocol, an application form for changes in confirmed items in a change management protocol, a notification form for minor changes in a change management protocol, and a notification form for changes made according to a change management protocol, a summary of changes related to the following applications or notifications and their dates should be filled in chronological order.

- Partial change approvals or minor change notifications after the first approval
- Applications for confirmation of changes in a change management protocol or notifications for changes in a change management protocol

Q10: Regarding the draft table for comparison between new and old application forms for approval defined in Section 2.2 (2) 1) of the PSEHB/MDED Notification, in the case where the most recent procedure for changes in approved items is performed with a minor change notification, may the "Old" field include the text that has reflected the concerned notification? Or should the text at the time of the last approval be included?

A10: If the most recent procedure for changes in the same major items as those included in the application for confirmation of a change management protocol is performed with a minor change notification, the "Old" field may include the text that has reflected the concerned notification. In this case, the field should be designed to clearly identify the items subject to the notification by underlining the relevant parts.

Q11: In the case where multiple changes are included in an application for confirmation of a change management protocol, how should the table for comparison between new and old texts be prepared?

A11: The table for comparison between new and old texts should be prepared in multi-level, side-by-side comparison format with reference to the example below. In the case where multiple changes included in the change management protocol are individually made by a separate notification for each change made according to the protocol, it should be noted that the table should be designed to compare the changes in the protocol with those made by notifications for changes made according to the protocol.

Example)

Item	Currently approved matter	New			Remarks
		Change 1)	Change 2)	Change 3)	
• • •	• • •	• • •	• • •	• • •	
Shape, structure, ingredients, quantities, or nature	●●●	XXX	No change	No change	To be addressed by Notification 1)
Manufacturing method	■■■	No change	□□□	No change	To be addressed by Notification 2)
• • •	• • •	• • •	• • •	• • •	

* Notification 1), To be submitted around MM YYYY
Notification 2), To be submitted around MM YYYY

Q12: Regarding Section 2.2 (2) 2) of the PSEHB/MDED Notification, if it is difficult to determine whether an application for confirmation of the compliance status of regenerative medical products is necessary at the time of an application for confirmation of a change management protocol, may the applicant determine whether the confirmation of the compliance status is necessary and enter the determination in the application form for confirmation of a change management protocol?

A12: Yes. Of note, the regulatory authority may instruct the applicant to change their entry for the necessity of an application for confirmation of the compliance status, if they determine that it should be changed during review of the change management protocol. The applicant may obtain PMDA's provisional view on the necessity of an application for confirmation of conformance status at a pre-consultation meeting before application, but it is finally determined based on the review, which should be noted.

3. Handling when a change management protocol is changed

Q13: In the case where non-minor changes are made to a confirmed change management protocol, does such a case require submission of a separate application for confirmation of a change management protocol? What happens with a relationship to the confirmed change management protocol?

A13: Depending on the extent of the change, either an application for confirmation of changes in the confirmed change management protocol or an application for confirmation of a separate change management protocol is required. The application for confirmation of changes in a change management protocol requires a procedure similar to that for a new application for confirmation of a change management protocol (it does not apply to the attached data). When confirmation is completed, a confirmation certificate for changes in change management protocol is issued. If a confirmed change management protocol is supposed to be completely changed, consultation with PMDA should be individually made.

4. Handling of changes made according to a change management protocol

Q14: Regarding Section 4.1 (1) 1) of the PSEHB/MDED Notification, do the study results and overview need to be in Japanese?

A14: If the original text is in languages other than Japanese and English, Japanese translation is required in principle. If the original text is in English, the overview prepared in Japanese is desirable.

Q15: In the case where some of the data attached to an application for confirmation of a change management protocol are in English, and an overview prepared in Japanese is attached, does a notification for changes made according to the change management protocol require attachment of the revised overview in Japanese?

A15: No.