PFSB Notification No. 0812-30
August 12, 2014

To each prefectural governor

Secretary-General of the
Pharmaceutical and Food Safety
Bureau, the Ministry of Health,
Labour and Welfare
(Official seal omitted)

Applications for Marketing Approval of Regenerative Medical Products

Applications for marketing approval of regenerative medical products, which are classified as drugs or medical devices, have been handled according to the "Applications for Approval of Drugs" (PFSB Notification No. 0331015, dated March 31, 2005, of the Pharmaceutical and Food Safety Bureau, the Ministry of Health, Labour and Welfare [MHLW]) or "Application for Marketing Approval of Medical Devices" (PFSB Notification No. 0216002, dated February 16, 2005, of the Pharmaceutical and Food Safety Bureau, MHLW). In line with the enforcement of 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"), amended by the "Act Partially Amending the Pharmaceutical Affairs Act" (Act No. 84 of 2013), handling of applications for marketing approval of regenerative medical products is specified in this document as shown below. Thank you for your understanding and efforts to ensure that specified provisions are properly applied.

This notification is effective as of November 25, 2014. For your information and guidance, this notification may be used as a reference for applications submitted for approval of regenerative medical products between the date of this notification and November 24, 2014.

Section 1 General Provisions

1. An approval of marketing of regenerative medical products is granted after the following process. When an application is submitted pursuant to the provisions of Article 23-25 of the Act by a person who intends to market regenerative medical products, data on the structure, constitutive cells, transgenes, regimen, doses, method of use, indication or performance, defects, etc. of the regenerative medical products are reviewed as necessary, and then the Minister of Health, Labour and Welfare grants an approval for each of the regenerative medical products. For applications for approval, data confirmed to be ethical, scientific, and reliable based on the academic standards of medicine, pharmacy, engineering, etc. of the time need to be submitted to support the basis adequately to demonstrate or estimate the quality, efficacy, and safety of the regenerative medical product to be proposed.

2. The terms used in this notification are as follows:

(1) The term “Enforcement Order” refers to the “Order for Enforcement of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices” (Cabinet Order No. 11 of 1961) amended pursuant to the provisions of the “Cabinet Order for Development of Relevant Cabinet Orders and Transitional Measures Associated with the Enforcement of the Act Partially Amending the Pharmaceutical Affairs Act” (Cabinet Order No. 269 of 2014).

(2) The term “Enforcement Regulation” refers to 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 [MHW] Ordinance No. 1 of 1961) amended pursuant to the provisions of the “Ministerial Ordinance for Development of Relevant Ministerial Ordinances Associated with the Enforcement of the Act Partially Amending the Pharmaceutical Affairs Act and the Cabinet Order for Development of Relevant Cabinet Orders and Transitional Measures Associated with the Enforcement of the Act Partially Amending the Pharmaceutical Affairs Act (MHLW Ordinance No. 87 of 2014).

(3) The term “Regenerative medical products” refers to those listed in Article 1-2 of the Enforcement Order (Appended Table 2) in accordance with Article 2, Paragraph 9 of the Act. Regenerative medical products are comprised of new regenerative medical products and other regenerative medical products.

(4) The term “New regenerative medical products” refers to new regenerative medical products specified in Article 23-29, Paragraph 1, Item 1 of the Act.

(5) The term “Other regenerative medical products” refers to regenerative medical products for which the reexamination period has been completed.

(6) The term “Regenerative medical products with new regimen or method of use” refers to new regenerative medical products that have the same structure, constitutive cells, and transgenes as those of the approved regenerative medical products but are used according to a different regimen (route of administration such as subcutaneous injection or intravenous administration) or a method of use (transplant site, transplant procedure, etc.).

(7) The term “Regenerative medical products with a new indication” refers to new regenerative medical products that have the same structure, constitutive cells, and transgenes as those of the approved regenerative medical products but have different indications or performances.

(8) The term “Regenerative medical products with a new structure” refers to new regenerative medical products that have the same constitutive cells, transgenes, and indication or performance as those of the approved regenerative medical products but have a different structure (physical characteristics of the product) given by changes to sub-ingredients (non-cellular and non-genetic ingredients such as scaffolds).

(9) The term “Regenerative medical products with new doses” refers to new regenerative medical products that have the same structure, constitutive cells, transgenes, indication or performance, and regimen or method of use as those of the approved regenerative medical products but are used at different doses.

(10) The term “Regenerative medical products with additional specifications” refers to other regenerative medical products that have the same structure, constitutive cells, transgenes, regimen, doses or method of use, and indication or performance as those of the approved regenerative medical products but have different specifications or contents of the packaging units.

Section 2 Data to be Attached to Application Forms for Marketing Approval

1. Studies used to prepare data to be attached to application forms for marketing approval

must comply with the "Ministerial Ordinance on Good Laboratory Practice (GLP) for Nonclinical Safety Studies of Regenerative Medical Products" (MHLW Ordinance No. 88 of 2014. Hereinafter referred to as "GLP") and the "Ministerial Ordinance on Good Clinical Practice (GCP) for Regenerative Medical Products" (MHLW Ordinance No. 89 of 2014. Hereinafter referred to as "GCP") and be properly conducted at facilities with adequate equipment based on the academic standards of medicine, pharmacy, engineering, etc. of the time by experienced researchers. The data prepared from the study results to be attached to the application forms for marketing approval must be collected and prepared in accordance with provisions of Article 137-25 of the Enforcement Regulation.

2. In principle, the data to be attached to application forms for marketing approval must be written in Japanese. However, if the data to be attached are in English, they may be directly attached in their original text, but a summary prepared in Japanese should be attached in principle.
3. Guidelines for studies conducted to prepare the data to be attached to application forms for marketing approval and handling of the data should be specified separately as needed.
4. The content for each item of Article 137-23, Paragraph 1 of the Enforcement Regulation should generally correspond to the data listed in the right column of Appended Table 1.
5. The data to be attached to application forms for marketing approval should cover the items indicated in the right column of Appended Table 2 according to the applicable category in the left column of the same table, in principle. If the applicable category is difficult to identify, the category requiring data on more items should be chosen. If more than one category is applicable, the data required for each of the categories should be attached. However, if a study for preparation of the data is technically infeasible and is considered insignificant in view of the type and method of use of the concerned regenerative medical product, attachment of the concerned study results may be omitted by presenting the above justification in the data summary specified in 6.
6. For an application for marketing approval, the data summary should be submitted in addition to the attached data. The data summary should include an accurate and concise overview of the attached data as well as information on the indication or performance and regimen, doses or method of use, draft package insert, and reasons for their establishment. Instructions on how to organize the data summary will be provided separately. In principle, the data summary must be written in Japanese.
7. If during the reexamination period of a new regenerative medical product (for approvals with conditions and time limit specified in Article 23-26 of the Act, including the period to the disposition specified in Paragraph 6 of the same article), an application of a regenerative medical product that has the structure, constitutive cells, transgenes, regimen, doses, method of use, and indication or performance potentially identical with those of the new regenerative medical product is submitted, the data equivalent to or more than those for the relevant new regenerative medical product will be required.
8. For an application for approval of partial changes in approved items (hereinafter referred to as application for partial change approval) based on Article 23-25, Paragraph 9 of the Act, a part of the data to be attached may not have to be attached according to the reason.
9. If an additive that has not been used as an excipient in approved drugs, etc. is to be used as a measurable constitutive ingredient of the regenerative medical product, data on the quality and safety of the constitutive ingredient should be additionally submitted.

10. For an application for approval of the new regenerative medical product that is resubmitted within the period specified in the previously obtained approval with conditions and time limit, a portion of the data that overlap with those attached to the initial application, which led to the approval with conditions and time limit, may not have to be submitted, but the data relating to changes made after the approval with conditions and time limit, if applicable, should be submitted for each item.

Section 3 Others

1. The proposed new regenerative medical products should be subject to qualifications for designated regenerative medical products in addition to approval review.
2. If an approval with conditions and time limit is granted pursuant to the provisions of Article 23-26 of the Act, the conditions and time limit should be determined in view of the comments raised at the Pharmaceutical Affairs and Food Sanitation Council in addition to the approval review.

Appended Table 1

Items in Attached Data and Corresponding Sections in Data Summary

Left column	Right column
1 Origin or History of Discovery and Usage Conditions in Foreign Countries, etc.	a Origin or History of Discovery b Usage Conditions in Foreign Countries c Comparisons with Other Similar Therapies
2 Manufacturing Method and Specifications	a Structure, Constitutive Cells, and Transgenes of the Products b Raw Materials, Materials to be Used, or their Source Materials c Manufacturing Method d Specifications
3 Stability	Rationale for Transportation, Storage Conditions, and Shelf Life
4 Indication or Performance	Primary Efficacy or Performance Studies
5 Biological Disposition of Product	a Biodistribution b Other Biological Disposition
6 Nonclinical Safety	a General Toxicity b Other Safety
7 Clinical Studies	Clinical Studies
8 Risk Analysis	a Risk Management Plan b Post-marketing Use-results Survey Plan c Clinical Study Plan to be Implemented
9 Items listed in the Package Insert Specified in Article 65-3, Paragraph 1 of the Act	a Draft Package Insert b Indication or Performance, Regimen and Doses or Method of Use, Precautions for Use (draft) and Rationales for their Establishment

Note) For combination products, additional data may be required according to attributes of the components included in the product.

Appended Table 2

Items that should be Covered by the Attached Data for Application

Left column	Right column								
	1 abc	2 abcd	3	4	5 ab	6 ab	7	8 abc	9 ab
(1-1) Application for approval of new regenerative medical products	○○○	○○○○	○	○	○△	○○	○	○○△	○○
(1-2) Application for approval of new regenerative medical products resubmitted within the period specified in the previously obtained approval with conditions and time limit	○○○	△△△△	△	△	△△	△△	○	○○△	○○
(2) Application for approval of regenerative medical products with new regimen or method of use	○○○	×△△△	△	○	○△	△△	○	○○△	○○
(3) Application for approval of regenerative medical products with new indication	○○○	××××	×	○	××	××	○	○○△	○○
(4) Application for approval of regenerative medical products with a new structure	○○○	○○○○	○	○	○△	○△	△	○○△	○○
(5) Application for approval of regenerative medical products with new doses	○○○	××××	×	△	△×	××	△	○○△	○○
(6) Application for approval of regenerative medical products with additional specifications	○○○	×○○○	○	△	××	××	×	○○△	○○
(7) Other regenerative medical products	○○○	○○○○	○	△	△△	△△	△	△△△	○○

Note) The symbols and numbers in the right column indicate the data items specified in Appended Table 1. In principle, ○ means that the data on this item should be attached; × means that the data on this item may not have to be submitted; and △ means that whether the data on this item should be submitted or not will be determined for individual regenerative medical products. For combination products, additional data may be required according to attributes of the components included in the product.