PFSB/ELD/OMDE/CMS Notification No. 0812-5
August 12, 2014

Attention to: Commissioner of Prefectural Health Supervising Department

Counsellor of Minister's Secretariat of the
Ministry of Health, Labour and Welfare
(for Medical Device and Regenerative Medicine
Product Evaluation)
(Official seal omitted)

Points to Consider for Applications for Marketing Approval of Regenerative Medical Products

Handling of marketing approvals of regenerative medical products pursuant to the provisions of Article 23-25 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) has been notified through 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]. Hereinafter referred to as "PFSB Notification"). Handling of the details are specified in this document as shown below. Please understand them, ensure that related organizations and institutions under your jurisdiction are thoroughly informed of them, and provide appropriate instructions to ensure that they are properly applied.

Section 1 General Provisions

The terms are defined as follows:

1. The term "Human cell processed products" fall within the scope specified in Article 1-2 (Appended Table 2) of 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. Hereinafter referred to as "Enforcement Order") 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) and refer to regenerative medical products in which the main constitutive cells essentially determining the indication or performance of the product are cells or tissues collected from humans or processed materials of the cells or tissues collected from humans.
2. The term "Animal cell processed products" fall within the scope specified in Article 1-2 of the Enforcement Order (Appended Table 2) and refer to regenerative medical products in which the main constitutive cells essentially determining the indication or performance of

the product are cells or tissues collected from animals or processed materials of the cells or tissues collected from animals.

3. The term "Processing" refers to manipulations for the purpose of disease treatment or tissue repair or reconstruction, including artificial proliferation and differentiation of cells and tissues, establishment of cell lines, treatment of cells and tissues with drugs for cell activation, modification of biological properties, combination with non-cellular ingredients, and genetic engineering. Of note, the following manipulations are not deemed as "Processing": separation of tissue, mincing of tissue, separation of cells, isolation of specific cells (excluding those separated by biological or chemical treatment with drugs, etc.), treatment with antibiotics, washing, sterilization by gamma rays, freezing, and thawing (provided, however, that this does not apply to the manipulations making the cells have a structure or exert a function different from that of the original cells).
4. The term "Gene therapy products" fall within the scope specified in Article 1-2 of the Enforcement Order (Appended Table 2) and refer to regenerative medical products comprised of expression constructs in which the genes essentially determining the indication or performance of the product are incorporated and expressed in a human or animal body other than human or animal cell processed products.
5. The term "Combination products" refer to products that combine at least 2 different types of drug agents, instruments, and processed cells (hereinafter referred to as "Drug agents, etc."), which would be classified as drugs, medical devices, and regenerative medical products if distributed alone, and are marketed as united drugs, medical devices, or regenerative medical products. In this notification, a group of combination products comprised of components that can be independently distributed including kit products are referred to as "combination products (set products)," while a group of ones comprised of components that are integral with drug agents or instruments are referred to as "combination products (other than set products)."
6. The term "Components" in a combination product (set product) refer to individual units packed in one primary package. Of components in a combination product (set product), one that essentially determines the indication or performance is referred to as the "main component," and ones that are not integral with the main component are referred to as the "sub-components."

Section 2 Items required to be entered on Application Forms for Marketing Approval

Unless otherwise specified, an application form for marketing approval of regenerative medical products should include the following items in the provided columns.

1. Column of approval number

   If the product to be proposed is a regenerative medical product previously approved pursuant to Article 23-25 of the Act, the approval number given with the relevant approval should be entered.
2. Column of approval date

   If the product to be proposed is a regenerative medical product previously approved pursuant to Article 23-25 of the Act, the approval number given with the relevant approval should be entered.
3. Column of category

   Of categories listed in Article 1-2 of the Enforcement Order (Appended Table 2), one applicable to the regenerative medical product to be proposed should be identified based on the constitutive cells or transgenes essentially determining the indication or performance and entered in this column.

4. Column of name

(1) The non-proprietary name of the product should be provided only if it has been already established. If no non-proprietary name is available at the time of application, the column should be left blank. A regenerative medical product with no non-proprietary name established at the time of application should be given an appropriate non-proprietary name when it is approved.

(2) The brand name should be one that would not mislead users about the indication or performance of the regenerative medical product or cause health and hygiene hazards and that maintains the integrity of the regenerative medical product. In addition, names that suggest other uses are not permitted. In principle, one product (including a combination product) should have one name.

5. Column of indication or performance

Patients and diseases for which the product is indicated as well as the expected indications should be specified. For the products that are unlikely to have appropriate indications, the expected performance should be specified as necessary.

6. Column of shape, structure, ingredients, quantities, or nature

Overviews of the proposed regenerative medical product overall and each of the components as well as the shape, structure, constitutive cells, transgenes, and quantities such as cell numbers, including method of use and specifications, should be described. The following points should be noted for description.

(1) Specifications for constitutive cells should define characteristics of the biological structure and functions and be presented as separate specifications on appropriately selected items, such as morphological features, growth properties, biochemical indicators, immunological indicators, characteristic produced substances, and other appropriate indicators of genotype or phenotype.

(2) Specifications for transgenes should be presented as separate specifications that include their sequences, structural drawings (vector maps, etc.) with elements and functions, and properties.

(3) Descriptions on human cells and tissues or animal cells and tissues used as raw materials for constitutive cells should include their origin, details of safety measures against various infectious diseases that might be transmitted through the collected cells and tissues, and other matters deemed necessary from the viewpoints of ensuring the quality and safety, with reference to the description examples in Attachment 1.

(4) Descriptions on human- or animal-origin constitutive ingredients such as serum added to the culture medium or other ingredients that constitute the final product should include their origin, details of donor screening, methods of inactivation or removal of bacteria, fungi, and viruses in the manufacturing process, and other matters deemed necessary from the viewpoints of ensuring the safety, with reference to the description examples in Attachment 1.

(5) Descriptions on constitutive ingredients that are manufactured from bovine- or other animal-origin raw materials and constitute the final product should include names of the ingredients, names of animals such as bovine, country of origin, origin of the parts used, manufacturing method, and other measures to ensure the quality and safety, such as using materials sourced from healthy animals and preventing contamination in the manufacturing process with materials derived from animals affected by BSE and parts prohibited from being used, with reference to the description examples in Attachment 1.

7. Column of manufacturing method

The column of manufacturing method should be filled with the following points noted and with reference to the attachment of the "Guideline for Descriptions on Application Forms for Marketing Approval of Drugs, etc. under the Revised Pharmaceutical Affairs Law" (PFSB/ELD Notification No. 0210001, dated February 10, 2005, from the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare).

(1) Manufacturing method and related matters

a Preparation and control methods of starting raw materials or materials

Starting materials should be identified and described to ensure the quality of the intended product in view of the quality of the product to be manufactured and raw materials used as well as attributes of the manufacturing process. Raw materials that are commonly used as starting materials should be listed as follows:

1) Preparation of master cell bank

- Preparation of master cell bank, which is used as the starting material for constitutive cells and transgenes of the proposed regenerative medical product, should be described including the acquisition method, a history of the preparation, and the qualification of the original cells.
- If the preparation process of the master cell bank, which is used as the starting material or material, involves genetic transformation technology, preparation of the expression construct should be described including a history of the genes and structure.
- If the preparation process of the master cell bank, which is used as the starting material or material, involves use of feeder cells, the acquisition method and history of the subsequent preparation of the feeder cells should be described.
- If feeder cells from the master cell bank are used after start of manufacture of the proposed regenerative medical product using the starting material or material, the acquisition method of the original cells used to prepare the master cell bank of the feeder cells, a history of the subsequent preparation, and the qualification should be described.
- If a new master cell bank is established or added, the methods of establishment and control should be described in the manufacturing method part below.

2) If cells are collected from a donor every time the product is manufactured:

- If human cells or tissues are collected from a donor to prepare the starting raw material or feeder cells every time the product is manufactured and no cell banks are prepared, the method from the collection to shipment at the medical institution should be described in the column of regimen and doses or method of use, and the process after receipt of the collected human cells or tissues should be described in the column of manufacturing method.
- If animal cells or tissues are collected from donor animals to prepare the starting raw material or feeder cells every time the product is manufactured and no cell banks are prepared, the process after receipt of the animals should be described in the column of manufacturing method.

b Control method of master cell bank

Test items and criteria for qualification of the master cell bank, information on stability during storage, methods of renewals, and others should be described.

(2) Manufacturing method

a The process from receipt of starting raw materials or materials to storage of the final product should be described.

The following points should be noted for description.

1) For combination products (other than set products), the process from receipt of the raw materials or materials of the drug agents or instruments, used as ingredients or parts, to fabrication of components should be described.

2) For combination products (set products), the process from receipt of the raw materials or materials of the drug agents or instruments, used as ingredients or parts, through the storage should be described for each component.

3) If drugs or medical devices of which an approval or certification has been already granted or Marketing Notification has been submitted or drug substances registered in the drug master file are used as components, the process before their receipt for manufacture may be omitted by entering the brand name, approval number, certification number, marketing notification number, registration number, etc.

b Raw materials or materials

1) Main raw materials or materials used in the manufacturing process should be listed. Critical raw materials or materials that affect the quality of the product should be identified, and then the specifications on the certain attributes of the identified raw materials or materials should be established to ensure that the manufacturing process is conducted as intended. Of note, the following points should be described by referring to the separate specifications for the raw materials or materials. For the materials approved or certified as drugs, etc., only the approval number or certification number and the following points for ruminant-derived materials may be entered.

- If a culture medium or buffer solution, such as DMEM, RMPI, PMS, or HBSS, that has the composition in public domain and is free from human- or animal-derived ingredients or its equivalent is used as a material, its ingredients may be described in an abbreviated form.
- For human- or animal-derived materials (such as feeder cells and medium ingredients used in cell culture, including growth factors, cytokines, enzymes, and antibodies), separate specifications should be established, covering their origin, details of donor screening, methods of inactivation or removal of bacteria, fungi, and viruses in the manufacturing process, and other matters deemed necessary from the viewpoints of ensuring the safety, with reference to the description examples in Attachment 1.
- For ruminant-derived raw materials or materials, the country of origin (information on monthly age of the animals as needed), parts, information on TSE data where necessary, and other matters deemed necessary from the viewpoints of ensuring the safety should be described in addition to the above, with reference to the description examples in Attachment 1.

8. Column of specifications

(1) Specifications as well as methods for checking system suitability, etc. established based on results from validations for analytical procedures should be described, with reference to notifications mentioned in Section 5.

(2) If the specifications listed in official compendia in Japan, such as the Japanese Pharmacopoeia, are adopted, the description may be abbreviated by stating the relevant adoption.

9. Column of regimen and doses or method of use

(1) The regimen and doses or method of use should be described in the order of procedures.

(2) If the regenerative medical product is prepared at a medical institution just before use, the preparation method including operations deemed critical from the viewpoints of ensuring the quality and safety of the product should be described.
(3) If human cells or tissues are collected from a donor to be used as starting materials or feeder cells every time the product is manufactured, points in the collection method applied at the medical institutions should be provided.
(4) For combination products (set products), not only the regimen or method of use for each component but also the regimen or method of use of the components in combination should be provided.
(5) For sub-components of a regenerative medical product that are intended to be re-sterilized and used repeatedly (e.g., instruments or equivalent), that effect and the re-sterilization method should be described.

10. Column of storage conditions and shelf life
(1) Storage conditions and conditions should be described for each component.
(2) A shelf life should be provided to components that deteriorate with time and thus need to have a shelf life. For sub-components allowed to have a shelf life of longer than 3 years, the shelf life may not need to be provided.

11. Column of manufacturing site of the product to be marketed
(1) Of the manufacturing site for the manufacturing process described in the column of manufacturing method, the name, location, manufacturing business license or accreditation number, and license or accreditation category should be provided.
(2) For the manufacturing business license or accreditation of the relevant manufacturing site, if the application is pending, the effect should be stated.

12. Column of remarks
(1) The marketing business license number of the applicant, the license category, and the address of its principal office should be provided or if an application for the license is pending, the effect (including the address of its principal office) should be stated.
(2) The manufacturing flow should be attached.
(3) The application category should be provided according to Appended Table 2 of the PFSB Notification.
(4) Images of the product should be attached to ensure understanding of the product appearance and distinction of each component.
(5) Whether the product is classified as an orphan regenerative medical product or not should be clarified.
(6) If the product is proposed for a priority review, the effect should be stated.
(7) For the sub-components that are drug agents or instruments, state whether applications are simultaneously submitted with the relevant drugs or medical devices.
(8) Whether the application is for new application for replacement or not should be clarified.
(9) If stability testing is, the details should be provided.
(10) If face-to-face consultations at the Pharmaceuticals and Medical Devices Agency (hereinafter referred to as “PMDA”) have been utilized, the effect should be stated.

Section 3 Handling of Data to be Attached to Application Forms for Marketing Approval

The data to be attached to application forms for marketing approval (hereinafter referred to as "Attached data") are as shown in Appended Tables 1 and 2 of the PFSB Notification. Handling of the details and points to note in preparing the data is as follows. The data to be submitted should strictly comply with the provisions of Article 137-25 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 [MHW] Ordinance No. 1 of 1961, hereinafter referred to as "Enforcement Regulation") 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) and be prepared through precise and objective discussions.

Guidelines for preparing the attached data of regenerative medical products will be separately issued as the notification "Guideline for Preparation of the Data to be Attached to the Approval Application Forms for Applications for Marketing Approval of Regenerative Medical Products."

For combination products (set products), the meaning and necessity of distributing the components in combination should be explained. For the sub-components that are drug agents or instruments, it should be noted that individual explanations of or individual evaluation data on the relevant drugs or medical devices may be required.

1. Origin or History of Discovery and Usage Conditions in Foreign Countries, etc.

a Origin or History of Discovery

The history of the proposed regenerative medical product, extending from conception of the development to clinical use, should be briefly described in chronological order to ensure understanding of the history and development of the technology. The development of the relevant regenerative medical product should be explained, including relations to the above.

b Usage Conditions in Foreign Countries

1) Use (name of country with use, year of commencement of use by country, year of authorization in countries with an authorization system, approximate annual use by country, etc.) in foreign countries (including the country of manufacture for the regenerative medical products manufactured in foreign countries if applicable) should be provided.
2) For an application for partial change approval to the approved product, the status of use and defects in Japan should be also described.
3) For an application of regenerative medical products with use results in foreign countries, information on the occurrence of malfunctions (type of malfunctions, frequency, etc.) reported up to date from use of the products in foreign countries, including the original one with license, should be described.

c Comparisons with Other Similar Therapies

1) New features, improvements, differences, or similarities of the proposed regenerative medical products in comparison with the existing regenerative medical products or cell processed products of the same class should be provided using comparison tables.
2) The medical positioning and characteristics of the proposed regenerative medical products should be provided using figures and tables to mark a distinction from the other treatment options.

2. Manufacturing Method and Specifications

a Structure, constitutive cells, and transgenes of the products

The structure and attributes of the proposed regenerative medical products should be

described in detail. In particular, the description on the constitutive cells or transgenes should cover the structure and attributes of the cells or genes as well.

b Raw materials or materials to be used or their raw materials

1) The acceptance specifications for the cells, tissues, and genes that constitute the bases of constitutive cells and transgenes of the proposed regenerative medical products as well as the other raw materials or materials to be used for manufacture or their raw materials should be described along with rationales for the establishment.
2) If human- or animal-derived raw materials are used, status of the application of and compliance with the "Standards for Biological Raw Materials" (see Section 4) should be described as necessary.
3) If ruminant-derived materials are used, status of the application of and compliance with the "Standards for Ruminant-Derived Raw Materials" in the "Standards for Biological Raw Materials" should be described as necessary.
4) If cell banks are prepared, a history of the preparation and the control method should be described.

c Manufacturing Method

For the time being, the points listed below should be noted, and the "Guideline on Preparing Data Attached to Application Form for Approval Application of Manufacture or Import of a New Pharmaceutical" (PMSB/ELD Notification No. 899, dated June 13, 2001, from the Evaluation and Licensing Division, Pharmaceutical and Medical Safety Bureau, MHLW) should be also referred to.

1) The process from receipt of starting materials to storage of the final product should be described. For the component registered in the drug master file and its intermediate, the manufacturing site of the relevant component or intermediate may be provided.
2) For the combination products (set products) with an instrument corresponding to a sterilized medical device incorporated as a sub-component, certificates on the period of sterilization validation and sterilization parameters should be attached. However, if the component is approved or certified as a sterilized medical device, its attachment may be omitted.

d Specifications

3) The specification should be established based on quality attributes of the product, including items required to be controlled from the viewpoints of ensuring safety and efficacy consistently for each component. Such established specifications and the test methods should be provided.
4) Data on reasons for including the items in the specifications should be prepared. The above data should explain that the established specifications are adequately designed to ensure the quality, efficacy, and safety of the proposed product. The test methods established based on the results from validation of analytical procedures should be justified by presenting the relevant test results.

In addition, if official specifications in or outside Japan other than those listed in the official compendia in Japan are adopted, such adoption should be justified. In this case, the full text of the specifications may be required.

5) The container closure system should be described along with the data supporting the appropriateness.

3. Stability

For the time being, the rationale for transportation, storage conditions, and shelf life should be prepared with the points listed below noted and also with reference to the "Guideline on Preparing Data Attached to Application Form for Approval Application of Manufacture or Import of a New Pharmaceutical" (PMSB/ELD Notification No. 899, dated June 13, 2001, from the Evaluation and Licensing Division, Pharmaceutical and Medical Safety Bureau, MHLW).

(1) Studies should be conducted to evaluate stability such as changes over time of storage under actual conditions, and based on the results, the appropriate storage conditions and shelf life should be established.

(2) If studies to evaluate stability such as changes over time of storage under accelerated and stress conditions are meaningful, based on the results including ones from these studies, the appropriate storage conditions and shelf life should be established.

(3) For sub-components that are intended to be re-sterilized and used repeatedly, the durability against repeated sterilizations under the sterilization conditions should also be described with the status of use taken into account.

4. Indication or Performance

For the time being, data relating to primary efficacy or performance studies should be prepared with the points below noted and also with reference to the "Handbook for Preparation of Summary Technical Documentation Submitted in Applications for Marketing Approval for Medical Devices" (PFSB/ELD/OMDE Notification No. 0216003, dated February 16, 2005, by the Director of the Office of Medical Device Evaluation, Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, MHLW).

(1) Evaluation results supporting the primary efficacy or performance of the proposed regenerative medical products when administered or used in the body should be presented. Data on *in vitro* and *in vivo* studies used or conducted for the evaluation as needed and the results thereof should be attached.

5. Biological Disposition

For the time being, data relating to biological disposition should be prepared with the points below noted and also with reference to the "Guideline on Preparing Data Attached to Application Form for Approval Application of Manufacture or Import of a New Pharmaceutical" (PMSB/ELD Notification No. 899, dated June 13, 2001, from the Evaluation and Licensing Division, Pharmaceutical and Medical Safety Bureau, MHLW).

(1) Biodistribution

Evaluation results on distribution or localization of the proposed regenerative medical products when administered or used in the body should be presented. Furthermore, discussion on survival period or duration of the effect should be included if possible. Data on *in vitro* and *in vivo* studies used or conducted for the evaluation as needed and the results thereof should be attached.

(2) Other Biological Disposition

Evaluation results on the regimen or method of use of the proposed regenerative medical products in the body should be presented. Data on *in vitro* and *in vivo* studies used or conducted for the evaluation as needed and the results thereof should be attached.

6. Nonclinical Safety

For the time being, data relating to nonclinical safety should be prepared with the points below noted and also with reference to the "Guideline on Preparing Data Attached to Application Form for Approval Application of Manufacture or Import of a New Pharmaceutical" (PMSB/ELD Notification No. 899, dated June 13, 2001, from the Evaluation and Licensing Division, Pharmaceutical and Medical Safety Bureau, MHLW).

(1) General Toxicity

Evaluation results on general toxicity of the proposed regenerative medical products when administered or used in the body should be presented. Data on *in vitro* and *in vivo* studies used or conducted for the evaluation as needed and the results thereof should be attached.

(2) Other Safety

Evaluation results on the safety other than the general toxicity of the proposed regenerative medical products should be presented. Data on *in vitro* and *in vivo* studies used or conducted for the evaluation as needed and the results thereof should be attached.

7. Clinical Studies

For the time being, data relating to results from clinical studies conducted should be prepared with the points below noted and also with reference to the "Handbook for Preparation of Summary Technical Documentation Submitted in Applications for Marketing Approval for Medical Devices" (PFSB/ELD/OMDE Notification No. 0216003, dated February 16, 2005, by the Director of the Office of Medical Device Evaluation, Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, MHLW].

(1) Data relating to clinical study results to be attached should include clinical study results enabling confirmation or estimation of the efficacy and evaluation of the safety of the proposed regenerative medical products as well as a summary of the evaluation results.

(2) For a study conducted multiple times, if any, not only the data relating to study results in each session but also comprehensive evaluation results on study results in the multiple sessions should be added to the data to be attached.

(3) To clinical study reports submitted as data relating to clinical study results, the protocol and case report form sample included in the appendices should be attached. Other appendices may not need to be incorporated generally but should be made readily available upon request from the reviewing authority.

8. Risk Analysis

For the time being, the points listed below should be noted, and the "Handbook for Preparation of Summary Technical Documentation Submitted in Applications for Marketing Approval for Medical Devices" (PFSB/ELD/OMDE Notification No. 0216003, dated February 16, 2005, by the Director of the Office of Medical Device Evaluation, Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, MHLW) should be also referred to.

(1) Risk Management Plan

The risk analysis system and plan to ensure that hazards and potential hazards identified in clinical trials of the proposed regenerative medical products will be analyzed and evaluated in post-marketing settings should be described.

(2) Post-marketing Use-results Survey Plan

The draft post-marketing use-results survey plan for the proposed regenerative medical products should be attached.

(3) Clinical Study Plan to be Implemented

If a clinical study is planned to be conducted in post-marketing settings, a draft protocol of the clinical study to be conducted should be prepared with reference to the guidelines for preparation of protocols and attached.

Section 4　Handling of Omission of Attached Data

1. Products approved with conditions and time limit

If a regenerative medical product approved with conditions and time limit pursuant to Article 23-26 of the Act has achieved the conditions, and then an application for marketing approval of the relevant product is submitted, a part of the attached data without additions or updates may be omitted.

2. Application for partial change approval

For applications for partial change approval pursuant to Article 23-25, Paragraph 9 of the Act, a part of the attached data without additions or updates may be omitted.

3. Combination products

For the combination products (set products) using instruments as sub-components, the evaluation data on shelf life may not need to be submitted unless special storage conditions or materials are used, and the shelf life should be established with the in-house guarantee. In doing so, however, a written statement to the effect that the shelf life is with the in-house guarantee should be attached.

4. Non-cellular and non-genetic sub-ingredients (refer to components other than drugs and medical devices)

In principle, for regenerative medical products, submission of evaluation data on nonclinical safety of the components is required, but the points listed below should be noted.

(1) For sub-ingredients (non-cellular and non-genetic materials) such as scaffolds for human and animal cell processed products, if the evaluation data on nonclinical safety of the relevant regenerative medical product allow evaluation of non-cellular and non-genetic materials, data on these materials alone (biological safety study results, etc.) may be omitted.

(2) If sub-ingredients of a regenerative medical product are added during a product formation process to maintain the shape of the product or to achieve the other purposes (refer to non-cellular and non-genetic materials added to the final product in a measurable manner. Hereinafter referred to as “Excipients”), and the relevant excipients have no precedent of use in drugs, etc., the evaluation data from nonclinical safety studies of the relevant sub-ingredients should be submitted in principle.

(3) Irrespective of (2), if the excipient has been used as a pharmaceutical excipient and thus has the appropriate safety evaluation data in view of the method of use, or the excipient is difficult to be evaluated for the safety by itself (e.g., adjuvant); for example, it is expected to exert the effect through interactions with the main ingredient, and the evaluation data on non-clinical safety of the components are available for the safety evaluation, submission of the evaluation data from nonclinical safety studies of the individual sub-ingredients corresponding to the new excipients will not be required.

Of note, because the safety of excipients in regenerative medical products is evaluated in view of the administration method and treatment period as well as target diseases of individual proposed products, their use in regenerative medical products as sub-ingredients shall not be deemed as precedent of use of the excipients in drugs or medical devices in principle.

Section 5　Guidelines for studies, etc.

For the guidelines relating to regenerative medical products, Attachment 2 should be referred to. In these guidelines, “cell and tissue processed products, etc.” and “gene therapy products” should be replaced with “regenerative medical products.” Procedures not presented in these

guidelines may be used only if they are based on rational grounds reflecting academic advances. It should be noted that these guidelines will be revised or superseded by new ones as necessary.

Section 6 Handling of Attached Data, etc. in Joint Development

1. If multiple parties jointly proceed with development of a new regenerative medical product, and conditions provided in (1) and (2) below are met, a group of the relevant multiple parties (hereinafter referred to as "Joint Development Group") should allow all or a part of the group members to use the data prepared by the other group members when submitting an application for marketing approval of the relevant new regenerative medical product.
   (1) An agreement has been concluded between the parties that each member of the Joint Development Group can use all the data created by any member other than the relevant member (including data supporting the relevant data) and that the storage manager ensures cooperation of any member other than the relevant member through the implementation.
   (2) A duplicate copy of the agreement specified in (1) above should be submitted with the application for marketing approval.
2. If more than one party of the Joint Development Group submits an application for marketing approval of the new regenerative medical product involved in joint development, whether each applicant should prepare the attached data or not will be determined according to the details of the joint development and the extent to which the products are identical. The applicants should consult with PMDA for each type of the attached data on a one-by-one basis.
3. Even if some parties of the Joint Development Group do not submit an application for marketing approval of the new regenerative medical product involved in the joint development, such non-applicants are subject to Article 137-25 of the Enforcement Regulation.
4. If more than one party submits an application for the same regenerative medical product at the same time, a relationship among the relevant multiple applications and differences in application data among them should be clarified, and the data proving that the proposed products are the same should be attached.

Section 7 Compilation method of application data

1. In accordance with Appended Table 2 of the PFSB Notification, a duplicate copy of the complete application form should be attached as the data for review at the time of application. The data should be compiled as provided below in principle.
   (1) Transmittal form of data for review (see Attached Form 1)
   (2) Application form for marketing approval (duplicate copy)
   (3) "Module 2 Data Summary" of the data attached to application forms for marketing approval described in the separately issued "Guideline for Preparation of the Data to be Attached to the Approval Application Forms for Applications for Marketing Approval of Regenerative Medical Products"
   (4) List of attached data
   (5) Attached data (data specified in Appended Table 1 of the PFSB Notification)
   (6) Certification Documents (duplicate copy of the joint development agreement, etc.)

(7) Other reference data

2. The following points should be noted during data compilation.

(1) Unclear photos such as ones of chromatograms in the data on specifications and ones of tissues in the clinical and toxicity data, if any, should be separately submitted in uncompressed electronic form.

(2) Other reference data should include the data at the time of preceding approval for re-applications for approval of the regenerative medical products previously approved with conditions and time limit and for applications for partial change approval to methods of use, indications, or doses of the previously approved regenerative medical products (duplicate copy of the approval certificate, review report, data summary, and list of attached data) as well as data on the documented PMDA clinical trial consultations, if applicable.

Section 8 Handling during approval reviews

1. Handling of manufacturing scale in attached data for new applications for marketing approval

(1) To establish and fill in the columns of manufacturing method and specifications, the data submitted for approval applications should be collected with manufacturing equipment at a scale corresponding to the commercial production, but the data obtained with manufacturing equipment for the commercial production may not need to be submitted.

(2) Even in the case of (1) above, the final manufacturing method for the commercial production should be established wherever possible, including process parameters and control criteria or values for critical steps and intermediates, before inspection specified in Article 23-25, Paragraph 6 of the Act (hereinafter referred to as "GCTP compliance inspection"), which is implemented before approval of regenerative medical products. The data on the established manufacturing method should be submitted to PMDA with the data on manufacture. In addition, since the GCTP compliance inspection requires the data obtained with manufacturing equipment for commercial production, an application for the GCTP compliance inspection should be submitted with the timing taken into account.

2. Handling of procedures, etc. in approval review

In approval review of regenerative medical products, the matters subject to applications for partial change approval and minor change notifications, which are specified by the applicant and provided in the column of manufacturing method in the approval application form, will also be reviewed.

3. Handling of procedures, etc. for changes to manufacturing method

(1) Any change to the manufacturing method for a regenerative medical product, regardless of the extent of the impact on quality and whether the change is applicable to an application for partial change approval or minor change notification, should be supported by appropriate validation and change control. That is, the change should be made based on the ground leading to judgment that the change control implemented in accordance with the GCTP ensures intact quality relating the efficacy and safety.

(2) Whether the change is applicable to minor change notification or not should be determined on a case-by-case basis with reference to examples in (8).

(3) Whether a matter should be handled as one subject to applications for partial change approval or not should be determined by the applicant with understanding of the relevant manufacturing method. However, the following cases may be subject to PMDA consultations on the target product.

a Appropriateness of the protocol for assessment implemented for the change
b Appropriateness of the judgment that intact quality is ensured, made based on results from studies conducted in accordance with the protocol
c Other matters requiring consultations for changes in the column of manufacturing method

Of note, if a step established as the matter subject to minor change notifications undergoes a change control procedure, and the impact of the change on quality is found different from that at the time of establishment, for example, obtained results reveal that the impact on the quality relating to efficacy and safety cannot be ruled out, any of the following actions should be taken: discontinuation of the relevant change, reconsideration, an application for partial change approval, or an application for approval handling the post-change product as a new product. As necessary, questions about the change, if any, should be brought in consultations with PMDA.

(4) For minor change notifications, a comparison table between the pre-change and post-change conditions should be submitted as reference data to clarify details of the changes as done for applications for partial change approval. The minor change notification should cover only the changes, and the applicant should submit a written statement to the effect that appropriate validation and change control have been implemented.

(5) The time of a change in a minor change notification can refer to the time either when the change is made or when the product manufactured in the post-change process is released, and the choice should be made by the marketing authorization holder according to details of the change. However, appropriate measures should be taken to ensure release of the product as specified in the post-change approval certificate.

(6) If a GCTP compliance inspection reveals that the change in the manufacturing process essentially not subject to minor change notifications has been made with a minor change notification, the relevant notification may be invalidated, charging the applicant with violation of the Act. In this case, the products already manufactured or marketed by the post-change method will be subject to suspension of release, recall, or other necessary administrative measures in view of the risk of the relevant change. If an inspecting authority questions whether the change is subject to applications for partial change approval during the GCTP inspection, the inspecting authority will communicate with the reviewing authority of the relevant product.

(7) A minor change notification may be submitted while an application for partial change approval is pending. However, in this case, the application form for partial change approval should be replaced to include all the matters relating to the minor change notification.

(8) To determine whether a change to the manufacturing method is subject to applications for partial change approval or minor change notifications, the following should be referred to.

Changes to the matters listed in the column of manufacturing method all require appropriate change control and thus are subject to applications for partial change approval in principle. However, in the following cases where the change is obviously deemed and confirmed to have potentially little adverse impact on quality and safety of the final product, it may be subject to minor change notifications.

a Where a change is made to an acceptable range of process parameters proposed at the time of application according to the process of the approval review or subsequently obtained production results;
b Where a change is made to an internal in-process control test and corresponding target values;
c Where a change is made to the scope of the manufacturing process within the same manufacturing site;

d Where a change is made to the country of origin relating to BSE to official compendia or according to other administrative procedures or where a change reasonably determined to have no adverse impact on product quality such as narrowing the acceptance criteria is made; and

e Where a change is made to the country of origin for human- or animal-derived raw materials to address a new risk of infectious agents, etc. or where a change is made according to other administrative procedures, as instructed by the reviewing authority.

In addition, among the standard batch sizes or the process parameters that serve as target values/set values, the matters to be addressed in a minor change notification shall be enclosed in 『 』, and those to be addressed in a partial change approval application shall be enclosed in 《 》. Furthermore, the matters to be addressed in a minor change notification other than target values/set values shall be enclosed in " ".

4. Handling of drug master file

If an application for registration in the drug master file specified in Article 80-6, Paragraph 1 of the Act is submitted, descriptions in the application form for registration should be handled as instructed in 2 above.

Section 8 Transitional Measures

1. On and after the date of this notification, applications for marketing approval of regenerative medical products according to the PFSB Notification and this notification may be submitted.
2. Prior laws continue to govern the application forms and attached data for cell and tissue processed products and gene therapy products that are submitted as those of drugs or medical devices by November 25, 2014. However, when the marketing business license of regenerative medical products is renewed after obtainment of the marketing approval, the marketing authorization holder should submit a notification of description update in the approval certificate (hereinafter referred to as the "Description update notification of approval certificate") according to the PFSB Notification and this notification.

(1) When a person who obtained a marketing business license on or before November 24, 2014 (hereinafter referred to as "Marketing authorization holder, etc.") renews the marketing business license for regenerative medical products by the end of the license period, the marketing authorization holder, etc. should submit the Description update notification of approval certificate to the Minister of Health, Labour and Welfare to ensure that the cell and tissue processed products already approved and marketed comply with the matters in the approval certificate for each product, as required for the marketing approval.

(2) In the case where an application for marketing approval was submitted on or before November 24, 2014, but the license period in (1) reaches the end between November 25, 2014 and an approval of this application, the Description update notification of approval certificate should be submitted promptly after the approval of the relevant application.

(3) If an application for partial change approval or a minor change notification is submitted before submission of the Description update notification of approval certificate associated with renewal of the business license according to the Act, the entire text in the approval certificate, not limited to the parts relating to the relevant change, should be updated to be consistent with the matters in the application form for marketing approval of regenerative medical products.

(4) Even if the description update has been completed in the case of (3), a Description update notification of approval certificate should be submitted at the time of business license renewal. In this case, details of the update may not need to be described again, and the time of completion of the update may be provided in the column of remarks.

(5) The Description update notification of approval certificate should be submitted through electronic means such as FD.

(6) The Description update notification of approval certificate should be prepared using Attached Form 2.

(7) A marketing approval of regenerative medicine products granted on or before November 24, 2014 is deemed to be an approval prescribed in Article 23-25 or Article 23-37 of the Act on and after November 25, 2014, pursuant to Article 30 or Article 37 of the Supplementary Provisions of the Act.

Attachment 1

1. Human cells and tissues (allogeneic)

(Name of ingredient ○○○) is derived from the human (sampling site). The relevant ingredient has been qualified through donor screening (describe the inspection items and inspection methods performed) for persons providing the raw material.

2. Raw materials derived from human blood

(Name of ingredient ○○○) is derived from blood collected in (country of blood collection). Blood collected in the following countries and blood collection centers meets the definition of donated blood in PMSB Notification No. 0515020, dated May 15, 2003, of the Pharmaceutical and Medical Safety Bureau. (possible countries and centers of blood collection should be listed)

3. Raw materials derived from humans and animals

(Name of ingredient ○○○) is derived from (part of use) of human (or animal name in case of animal). The ingredient has been qualified through donor screening (describe the inspection items and inspection methods performed) for persons (or animal name in case of animal) providing the raw material and has been subjected to inactivation or removal treatment of pathogens according to ○○○○.

(Name of ingredient ○○○) is derived from (part of use) of human (or animal name in case of animal). The ingredient is derived from healthy humans (or animals), has been inspected for ○○○ (indicate which is applicable, raw material or process) (describe the inspection items and inspection methods performed), and has been subjected to inactivation or removal treatment of pathogens according to ○○○○.

4. Bovine- or other animal-origin raw materials

(Name of ingredient ○○○) is derived from (part of use△△△) in (animal name such as bovine) (country of origin). The manufacturing method should use raw materials that are specified in ○○ (or specifications in official compendia) and derived from healthy animals. △△△ should be collected with measures taken to prevent contamination in the manufacturing process with materials derived from animals affected by BSE and parts prohibited from being used specified in the “Standards for Ruminant-Derived Raw Materials” in the “Standards for Biological Raw Materials” and used as a raw material. (of note, the relevant raw materials, etc. meet the conditions specified in Section 2 (1) [2] of PMSB Notification No. 1069, dated October 2, 2001, of the Pharmaceutical and Medical Safety Bureau, pursuant to provisions in Paragraph 4 of the above standards)

Attachment 2

1. Guidelines for Human Cell Processed Products
   (1) Ensuring the Quality and Safety of Drugs, etc. Manufactured from Raw Materials of Human or Animal Origin (PMSB Notification No. 1314, dated December 26, 2000)
   *It should be noted that Attachment 2 was superseded by PFSB Notification No. 0912006, dated September 12, 2008.
   (2) Ensuring Quality and Safety of Products Derived from Processed Cell and Tissue (autologous cells) (PFSB Notification No. 0208003, dated February 8, 2008)
   (3) Q&A on Guidelines for Ensuring Quality and Safety of Products Derived from Processed Cell and Tissue (autologous cells) (Administrative Notice, dated March 12, 2008)
   (4) Ensuring Quality and Safety of Products Derived from Processed Cell and Tissue (allogeneic cells) (PFSB Notification No. 0912006, dated September 12, 2008)
   (5) Q&A on Guidelines on Ensuring Quality and Safety of Products Derived from Processed Cell and Tissue (allogeneic cells) (Administrative Notice, dated October 3, 2008)
   (6) Ensuring Quality and Safety of Products Derived from Human Processed Somatic Stem Cell (autologous cells) (PFSB Notification No. 0907-2, dated September 7, 2012)
   (7) Ensuring Quality and Safety of Products Derived from Human Processed Somatic Stem Cell (allogeneic cells) (PFSB Notification No. 09073, dated September 7, 2012)
   (8) Ensuring Quality and Safety of Products Derived from Human Processed iPS(-like) Cell (autologous cells) (PFSB Notification No. 0907-4, dated September 7, 2012)
   (9) Ensuring Quality and Safety of Products Derived from Human Processed iPS(-like) Cell (allogeneic cells) (PFSB Notification No. 0907-5, dated September 7, 2012)
   (10) Ensuring Quality and Safety of Products Derived from Human Processed ES Cell (PFSB Notification No. 0907-6, dated September 7, 2012)

2. Guidelines for Gene Therapy Products
   (1) Ensuring Quality and Safety of Gene Therapy Products (PFSB/ELD Notification No. 0701-4, dated July 1, 2013)

3. Guidance for the Evaluation of Emerging Technology Medical Devices
   (1) Publication of the Guidance Document for the Evaluation of Emerging Technology Medical Devices (cell sheet for cell therapy of severe heart failure, corneal epithelial cell sheets, etc.) (PFSB/ELD/OMDE Notification No. 0118-1, dated January 18, 2010)
   (2) Publication of the Guidance Document for the Evaluation of Emerging Technology Medical Devices (corneal endothelial cell sheet, etc.) (PFSB/ELD/OMDE Notification No. 0528-1, dated May 28, 2010)
   (3) Publication of the Guidance Document for the Evaluation of Emerging Technology Medical Devices (articular cartilage regeneration, etc.) (PFSB/ELD/OMDE Notification No. 1215-1, dated December 15, 2010)
   (4) Publication of the Guidance Document for the Evaluation of Emerging Technology Medical Devices (Cell Sheets for Treatment of Periodontal Tissues, etc.) (PFSB/ELD/OMDE Notification No. 1207-1, dated December 7, 2011)

(5) Publication of the Guidance Document for the Evaluation of Emerging Technology Medical Devices (retinal pigment epithelial cells, etc. derived from autologous iPS cells) (PFSB/ELD/OMDE Notification No. 0529-1, dated May 29, 2013)

4. Relating to Standards for Biological Raw Materials

(1) Standards for Biological Raw Materials (Public Notice of the Ministry of Health, Labour and Welfare No. 210 of 2003)

*Operations will be notified later.

5. Other Guidelines for Reference

ICH Guidelines

(1) Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin (ICH Q5A) (PMSB/ELD Notification No. 329, dated February 22, 2000)

(2) Quality Of Biotechnological Products: Analysis of the Expression Construct in Cells Used for Production of r-DNA Derived Protein Products (ICH Q5B) (PMSB/ELD Notification No. 3, dated January 6, 1998)

(3) Quality Of Biotechnological Products: Stability Testing of Biotechnological/Biological Products (ICH Q5C) (PMSB/ELD Notification No. 6, dated January 6, 1998)

(4) Derivation and Characterisation of Cell Substrates Used for Production of Biotechnological/Biological Products (ICH Q5D) (PMSB/ELD Notification No. 873, dated July 14, 2000)

(5) Comparability of Biotechnological/Biological Products Subject to Changes in their Manufacturing Process (ICH Q5E) (PFSB/ELD Notification No. 0426001, dated April 26, 2005)

(6) Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products (ICH Q6B) (PMSB/ELD Notification No. 571, dated May 1, 2001)