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PFSB/SD Notification No. 1002-13
October 2, 2014

To Commissioners of Prefectural Health Departments (Bureaus):

Director of Safety Division,
Pharmaceutical and Food Safety Bureau,
Ministry of Health, Labour and Welfare
(Official seal omitted)

Instructions for Package Inserts of Regenerative Medical Products (Detailed Rules)

With regard to the title, the "Act Partially Amending the Pharmaceutical Affairs Law, etc." (Act No. 84 of 2013, hereinafter referred to as the "Amendment Act"), "Cabinet Order on the Development of Relevant Cabinet Order and Transitional Measures with the Enforcement of the Act Partially Amending the Pharmaceutical Affairs Law, etc." (Cabinet Order No. 269 of 2014), and "Ministerial Ordinance on the Development of Relevant Ministerial Ordinances Associated with the Enforcement of the Act Partially Amending the Pharmaceutical Affairs Law, etc. and the Cabinet Order on the Development of Relevant Cabinet Order and Transitional Measures with the Enforcement of the Act Partially Amending the Pharmaceutical Affairs Law" (MHLW Ordinance No. 87 of 2014) were promulgated, and it was decided that regenerative medical products should be handled as a new category. Accordingly, PFSB Notification No. 1002-12 by the Director-General of Pharmaceutical and Food Safety Bureau (hereinafter referred to as "Director-General Notification"), dated October 2, 2014, has established the "Instructions for Package Inserts of

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Regenerative Medical Products." Regarding the detailed rules, please take note of the following points described in the attachment and inform the relevant organizations, etc. under your jurisdiction, giving particular consideration to instructions on package inserts of regenerative medical products as well.

This notification shall come into effect as of November 25, 2014.

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Attachment

Instructions for Package Inserts of Regenerative Medical Products (Detailed Rules)

1. General Considerations for Description

(1) Each item shall be described in an easy-to-understand manner after sufficiently examining the contents, and it is desirable to fill in all items as much as possible. However, if there is no appropriate information to describe, it is acceptable to omit the description including the "item name."

(2) When describing each item of "(2) Approval Number," "(3) Category and Nonproprietary Name, etc.," "(4) Brand Name," "(8) Indications or Performance," "(15) Precautions for Handling," and "(16) Approval Conditions and Time-Limits," documents attached at the time of marketing approval (hereinafter referred to as "approval") or the approved contents shall be correctly described.

(3) For each item from "(5) Warnings" to "(7) Shape, Structure, Ingredients, Quantity or Nature" and from "(9) Dosage and Administration or Methods of Use" to "(14) Storage Method and Shelf Life, etc.," the contents shall be the same as those of the documents attached at the time of approval or the approved contents. If all the contents to be described are unable to be stated, it is acceptable to create a summary of them and a note to refer to the instructions for use, etc.

(4) When describing each item from "(5) Warnings" to "(18) Name, Address, etc. of Marketing Authorization Holder (hereinafter referred to as "MAH"),” they shall be described with the names of the items specified. The names of the items shown in the Director-General Notification shall be used in principle.

(5) When describing each item of "(11) Clinical Studies," "(12) Principle/Mechanism," "(13) Pharmacokinetics," and "(14) Storage Method and Shelf Life, etc.," an accurate description based on scientific and highly credible literature, etc. is required in principle. In this case, the source shall be clarified. Use of expressions that may give the impression that the data are general facts despite the shown date being exceptional shall be avoided.

(6) When describing major items, such as item names, methods such as using Gothic font or increasing the font size shall be devised to secure visibility.

(7) Taking into consideration the convenience for healthcare professionals, the form/specification shall be A4 size in principle (1.7 cm of left binding margin shall be secured).
(8) When describing each item from "(5) Warnings" to "(18) Name, Address, etc. of MAH," consideration shall be given to visibility, such as using a font size of around 8 points, in principle, unless otherwise specified.
(9) For products for which instructions for use, etc. are prepared in addition to package inserts, the statement “the instructions for use, etc. shall be referred to” or similar shall be described in a prominent place on the first page of the package insert.

2. Points to consider for each description item
(1) "Year and Month of Preparation or Revision"
1) The year and month of preparation or revision and the version number shall be described in the upper left corner of the package insert.
2) When items that significantly affect the use of the regenerative medical product are revised, they shall be described by the following method.
[1] The year and month of preparation or revision shall be continuously presented until the revision after the next is made, the year and month of revision before the last (year and month of preparation for the time of the second revision) shall be deleted when describing the new year and month of revision, and the year and month of the new revision shall be added to the year and month of the last revision. In addition, the present revision and the last revision shall be separated and specified.
[2] For the revised part of description, for example, add "*" ahead of the item and underline the revised language so that the revised language can be identified easily. In addition, the same mark shall be put for the corresponding year and month of revision and the version number.
(2) "Approval Number, etc."
1) In principle, it shall be described on the right side of the brand name.
2) In principle, "Do not reuse" shall be described under the year and month of preparation or revision, as well as in the section of "Contraindications."

(3) "Category and Nonproprietary Name, etc."

1) In principle, the category and nonproprietary name shall be described in a highly visible place above the brand name (center).
2) It shall be described whether the product is a designated regenerative medical product or regenerative medical product ahead of the brand name.

   Example of description:

   Category
   Nonproprietary name
   Designated regenerative medical product XXX (brand name)
3) For regenerative medical products for which a conditional and time-limited approval was granted in Article 23, Paragraph 26, Item 1 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"), "Product with conditional and time-limited approval" shall be described on the right side of or below the brand name. If the condition is for a part of indications or performance, "Product with (partially) conditional and time-limited approval" shall be described. Regarding this description, it is acceptable to delete the description in the package insert upon satisfying the approval condition corresponding to the conditional and time-limited approval.
4) For regenerative medical products stipulated in Article 23-26-2, Paragraph 1 of the Act, "Caution: Regenerative medical product with emergency approval" shall be described on the upper or left side of the brand name, and the applicable part shall be encircled in red.
5) For regenerative medical products stipulated in Article 23-28, Paragraph 1 of the Act, "Caution: Regenerative medical product with special approval" shall be described on the upper or left side of the brand name, and the applicable part shall be encircled in red.

(4) "Brand Name"

1) The brand name shall be described in a conspicuous place in the center with letters larger than those of "Category and Nonproprietary Name, etc."
2) When more than one component is approved by a single approval and separate package inserts of the sub-components are prepared, each sub-component cannot be identified only by the brand name. Therefore,

a name other than the brand name shall be separately given as a suffix to identify each sub-component.

(5) "Warnings"

1) Warnings shall be described at the beginning of the text.

2) Details of the items shall be described according to PFSB Notification No. 1002-9 by the Director of the Safety Division, dated October 2, 2014, "Instructions for Precautions for Regenerative Medical Products" (hereinafter referred to as the "Director Notification").

3) As an exception for designated regenerative medical products, overall precautions regarding the risk of transmission of infections shall be described in a boxed column using a column spanning ahead of the section "(5) Warnings."

The specific expression shall be in accordance with Appendix 1.

[1] Ingredients derived from human or animal blood, cells, tissues, organs, etc. are used as raw materials, etc. (raw materials or constituent materials, or upstream raw materials of them (those from which raw materials or materials used for manufacturing are derived, the same shall apply hereafter) the same shall apply hereafter) or used in the manufacturing process.

[2] Safety measures to prevent transmission of infections are taken (describe specific safety measures in the section such as "Important Precautions" of "Precautions").

[3] The risk of transmission of infections cannot be completely eliminated.

(6) "Contraindications"

1) In principle, they shall be described following the “Warnings.” If there is no “Warnings” section, they shall be described at the beginning of the text.

2) Details of the items shall be described according to the Director Notification.

(7) "Shape, Structure, Ingredients, Quantity and Nature"

1) In consideration of the nature of the regenerative medical product, the form, structure, component cells, introduced genes, etc. shall be described.

2) In principle, illustrations, photos, etc. shall be shown for each component so that the overall structure of the regenerative medical product can be easily understood.

3) In addition to the main component to be used for the patient, for sub-components, such as machinery/equipment, etc. that directly contact the body (including cases where the machinery/equipment comes in contact with the body via drug solution, etc.), the composition of the parts that come into contact with the body shall be described.
4) Of the raw materials or constituent materials contained in the regenerative medical product or used in the manufacturing process, the names of human- or animal-derived ingredients, “human” or the name of animals as the raw materials of the product, the sites of use, etc. shall be described. When allogeneic human cells/tissues are used as raw materials (limited to designated regenerative medical products), the country where the allogeneic raw material is collected shall be described. If human blood is used as a raw material, the country where the blood is collected and the method of blood collection (blood donation or non-donation) shall be described.

However, for raw materials or constituent materials that are not covered by the Standard for Biological Ingredients (MHLW Notification No. 210, 2003), these descriptions are not required.

The specific description method shall be as follows.

[1] Of raw materials, etc., describe the name of the human- or animal-derived raw material, “human” or the name of animal from which the raw material is derived (e.g., human in the case of human, animal species in the case of animal), the site of use, etc. (e.g., blood in the case of blood, the names of cells, tissues, organs, etc. in the case of them) based on the description in the approval document.

[2] If any human- or animal-derived ingredient is used in the manufacturing process, describe the name of the ingredient, “human” or the name of the animal from which the ingredient is derived, the site of use, etc. in the same manner as above.

[3] When the product is manufactured using human blood as raw materials, describe the country where blood is collected (in principle, all countries described in the approval document as countries where blood is collected) and the method of blood collection (blood donation or non-donation).

[4] When the product is manufactured using allogeneic human cells/tissues as raw materials (limited to designated regenerative

medical products), describe the country where the allogeneic raw material is collected (in principle, all countries described in the approval document as countries where it is collected).

(8) "Indications or Performance"

1) Approved indications or performance (hereinafter referred to as "indications, etc.") shall be described.
2) For regenerative medical products for which reexamination/reevaluation has been already completed, indications, etc. shall be described based on the results of the reexamination/reevaluation, regardless of the above.
3) When there are precautions related to indications, etc., including patients to whom the product should be used, to prevent serious defects or adverse events, or accidents, they shall be described as "Precautions related to indications or performance" following this section by clearly separating them from the approved contents.
4) For products for which a part of the indications or performance corresponds to a specific regulatory category, such as regenerative medical products for which a conditional and time-limited approval in Article 23-26, Paragraph 1 was granted, annotation shall be given to the target indications or performance to clarify it.

(9) "Dosage and Administration or Methods of Use"

1) The approved dosage and administration or methods of use shall be described.

   For regenerative medical products for which reexamination/reevaluation has been already completed, they shall be described based on the results of the reexamination/reevaluation, regardless of the above.
2) When there are precautions related to the methods of use, etc., including dosage and administration, methods of use, and number, period, etc. of use, to prevent serious defects or adverse events, or accidents, they shall be described as "Precautions related to dosage and administration or methods of use" following this section by clearly separating them from the approved contents. In particular, the prohibited methods of use, including the limit of use of the product, shall be described in black letters in the red frame in the section of Contraindications.
3) It is desirable to add a graphical explanation as necessary.

4) In cases where the products are to be used in combination with other drugs, medical devices, etc., the requirements for the drugs, medical devices, etc. or those that can be used in combination shall be described.

(10) "Precautions"

1) They shall be described according to the Director Notification.
2) Of the "Precautions," when there are precautions related to indications or performance, including patients to whom the product should be used, to prevent serious accidents or adverse reactions, they shall be described as "Precautions related to indications or performance" following the item "Indication or Performance" by clearly separating them from the approved contents.
3) Of the "Precautions," when there are precautions related to dosage and administration or methods of use to prevent serious accidents or adverse reactions, they shall be described as "Precautions related to dosage and administration or methods of use" following the item "Dosage and Administration or Methods of Use" by clearly separating them from the approved contents.
4) Of the "Precautions," matters corresponding to "Warnings" "Contraindications," 2) and 3) do not need to be included in duplicate in this item in principle.
5) When describing "Important Precautions," "Precautions," and "Clinically Significant Defects/Adverse Reactions," consideration shall be given to make the descriptions easier to read compared to other items, such as using a font size of 8 points or larger.
6) As "Important Precautions," it shall be stated that when using the product, the efficacy and safety of the product and other matters necessary for its proper use should be explained to patients to whom the product is used, and that efforts should be made to obtain their consent before using the product.

   The specific expression shall be in accordance with Appendix 1 or 2. Other basic precautions specific to the product shall be described in this section.
7) For designated regenerative medical products, the details of infectious disease tests performed at the time of collection of raw materials, details

of inactivation treatment, limitations of safety measures, etc. shall be described in an appropriate part of the "Precautions."

(11) "Clinical Studies"

1) They shall be described only if there are results of clinical studies used at the time of the approval application or materials evaluated as substitutes for them, or clinical studies, etc. used at the time of the reexamination application.
2) The status of use, period, number of subjects, efficacy rate, etc. from the results of clinical studies that were conducted accurately and objectively shall be described in line with the approved method of use. The results of investigations appropriately planned and implemented using a medical information database shall be described by clearly specifying the source of the quotation.
3) Comparison with other drugs, medical devices, regenerative medical products, etc. may be described only when the treatment method using the control product is an ordinal method for the treatment of the disease, etc. and there are results of accurate and objective controlled studies.
4) Results suggesting "indications or performance" outside the scope of the application of the regenerative medical product shall not be described.

(12) Principle/Mechanism

The principle and mechanism by which the regenerative medical product is considered to exert its efficacy or performance shall be briefly described.

(13) Pharmacokinetic

If findings on biodistribution, engraftment period, duration of effect, etc. of the regenerative medical product are accumulated, they shall be described.

(14) "Storage Method and Shelf Life, etc."

1) Subsections both for the storage method and shelf life/expiration date of the regenerative medical product shall be prepared to describe them.
2) For the shelf life/expiration date, the usable period (number of days, hours, etc.) or the final expiration date for the use of the regenerative medical product (year/month (day)) shall be described.
3) Other precautions to confirm the quality before the use of the regenerative medical product shall be described if applicable.

(15) "Precautions for Handling"

1) If precautions for handling are specified in the standards or approval document, they shall be described.

2) For designated regenerative medical products, it shall be described that the brand name, manufacturing number or manufacturing code (lot number), date of use, and name/address, etc. of the patient using the products shall be recorded when the products are used and that the records shall be retained for at least 20 years. The specific expression shall be in accordance with Appendix 1.

(16) "Approval Conditions and Time-Limits"

1) They shall be described only when approval conditions and time-limits are given. If there is any change or extension in the approval conditions or time-limits, the description shall be revised.
2) It is acceptable to make a revision to delete the description after the approval condition is fulfilled. The description shall not be deleted until the approval condition is fulfilled.

(17) "References and Reference Request"

1) The name, address, and telephone number of the person/institution shall be described for reference requests.
2) Literature for key data supporting the description of each item shall be cited in this item as references. It is desirable to preferentially describe literature supporting the description of clinical studies (results of controlled studies, adverse reactions, etc.).
3) For the relevant part citing the contents of literature described as references, the reference number shall be given so that users can find the literature.
4) Literature suggesting "indications or performance" outside the scope of the application of the regenerative medical product shall not be described.

(18) "Name, Address, etc. of Marketing Authorization Holder"

1) The name, address, and telephone number of the MAH (including designated MAH) shall be described.
2) For the telephone number of the MAH, the number that can be contacted at all times in case of emergency shall be described.
3) It is desirable to prepare a column (blank column) for entering the contact information of the distributor (or agent) following this item.

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Appendix 1

Example of description of precautions at the beginning regarding the risk of transmission of infections for designated regenerative medical products

When human- or animal-derived cells are used
For this regenerative medical product, cells derived from "human" or the name of the animal and the name of the tissue, etc.[*1] are used. When collecting tissues, etc. as raw materials, a medical interview and infection-related tests are performed, and inactivation treatments at a certain level in the manufacturing process[*2], etc. are performed as safety measures to prevent transmission of infections. However, since the risk of transmission of infections due to the use of "human" or the name of animal and the name of the tissue, etc. as raw materials cannot be completely eliminated, this regenerative medical product shall be used to the minimum necessary after fully considering the necessity for the treatment of diseases. * 1) Describe "human" or the name of animal and the name of the tissue, etc. of the origin. * 2) Describe it if any processing is performed for the purpose of avoiding the risk of transmission of infections other than medical interview and infection tests when collecting blood, etc. as a raw material. *The underlined language shall be described according to the product.
When blood-derived ingredients, such as human serum albumin, are used during the manufacturing process
For this regenerative medical product, human serum albumin is used during the manufacturing process. When collecting blood as raw materials, a medical interview and infection-related tests are performed, and inactivation treatments at a certain level in the manufacturing process, etc. are performed as safety measures to prevent transmission of infections. However, since the risk of transmission of infections derived from human serum albumin remaining in the product cannot be completely eliminated, this regenerative medical product shall be used to the minimum necessary after fully considering the necessity for the treatment of diseases.

Note)

The details of cells/ingredients contained in products related to the risk of transmission of infections and the method of blood collection as a raw

material (blood donation or non-donation) shall be described in the section of "Shape, Structure, Ingredients, Quantity or Nature" (refer to the Director-General Notification 3 (7)). The details of infection tests, details of inactivation treatment, limitations of safety measures, etc. shall be described in appropriate sections, such as "Precautions."

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Example of description for explanation to patients in the section of Important Precautions in Precautions for designated regenerative medical products

"Explanation to patients"

When using this regenerative medical product, the necessity of this regenerative medical product for the treatment of diseases, the efficacy and safety of this regenerative medical product, other matters necessary for the proper use of this regenerative medical product, and the fact that the risk of transmission of infections derived from the use of human blood (/cell/tissue names, etc.) as a raw material cannot be completely eliminated although safety measures to prevent the transmission of infections have been taken in the manufacturing of the regenerative medical product shall be explained to patients, and efforts shall be made to obtain their consent before using this regenerative medical product.

Example of description for retention of records in the section of Precautions for Handling of designated regenerative medical products

"Retention of records"

Since this product corresponds to a designated regenerative medical product, the name of the regenerative medical product (brand name), its manufacturing number or manufacturing code (lot number), date of use, and name and address, etc. of the patient using the product shall be recorded when the product is used, and the records shall be retained for at least 20 years.

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Appendix 2

Example of description for explanation to patients in the section of Important Precautions in Precautions for regenerative medical products

"Explanation to patients"

When using this regenerative medical product, the necessity of this regenerative medical product for the treatment of diseases, the efficacy and safety of this regenerative medical product, and other matters necessary for the proper use of this regenerative medical product shall be explained to patients, and efforts shall be made to obtain their consent before using the regenerative medical product.