PSB/PSD Notification No. 0607-2
June 7, 2024

To: Commissioners of Prefectural Health Departments (Bureaus):

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

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

The above-mentioned matter has been notified through the “Instructions for Electronic Package Inserts of Regenerative Medical Products” (PSB Notification No. 0607-1 by the Director-General of Pharmaceutical Safety Bureau, Ministry of Health, Labour and Welfare (hereinafter referred to as “MHLW”) dated June 7, 2024) (hereinafter referred to as “Director-General Notification”). Points to consider for its operation have been organized as presented in the appendix. Please, therefore, make this Instruction thoroughly known to all relevant industries and organizations under your supervision with attention being paid to the below-mentioned points, and also make the necessary arrangements for appropriate instructions to be given regarding the package inserts for regenerative medical products.

1 Timing of implementation

The date of implementation of this notification shall be the same as that of the Director-General’s Notification.

2 Repeal of existing notifications

The “Instructions for Package Inserts of Regenerative Medical Products (Detailed Rules)” (PFSB/SD Notification No. 1002-13, by the Director of Pharmaceutical Safety Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare dated October 2, 2014) and the “Instructions for PRECAUTIONS of Regenerative Medical Products” (PFSB/SD Notification No. 1002-9, by the Director of Safety Division, Pharmaceutical and Food Safety Bureau, MHLW dated October 2, 2014) will be abolished and replaced with the contents herein.

Appendix

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

I. General Points to Consider for Drafting

1. Unless otherwise specified, in general, the heading shall follow the format in the “Instruction for Electronic Package Inserts of Regenerative Medical Products” (PSB Notification No.0607-1 dated June 7, 2024, by the Director-General of Pharmaceutical Safety Bureau, MHLW).
2. The section numbers listed in the Director-General Notification shall be used. When lower-level sections are established, sections down to the third level such as “1.1.1” may be created. If additional section numbers are needed, parentheses such as “(1)” shall be utilized.
3. When a related section is mentioned as a section that should be referred to, a section number shall be used, and it shall be at the end of the text, for example, “see Section 1.1.1.”
4. Information in each section shall be written in an easy-to-understand manner after sufficient consideration of its contents, and it is desirable to fill in all sections as much as possible. However, if no relevant information is available, it is acceptable to omit the description including the “ heading (section name),” but the section numbers should not be carried forward or changed.
5. When describing each section of “B. Approval Number,” “C. Category and Nonproprietary Name, etc.,” “D. Brand Name,” “4. INDICATIONS OR PERFORMANCE,” “6. DOSAGE AND ADMINISTRATION OR METHODS OF USE,” and “21. CONDITIONS FOR APPROVAL AND TIME-LIMITS,” documents attached at the time of marketing approval (hereinafter referred to as "approval") or the approved contents shall be correctly described.
6. The contents of each section from “1. WARNING” to “3. SHAPE, STRUCTURE, INGREDIENTS, QUANTITY OR NATURE,” and from “7. PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION OR METHODS OF USE” to “20. PRECAUTIONS FOR HANDLING” should be the same as the contents of the documents attached at the time of approval or the approved contents. (However, this does not apply to sections to be revised after the initial marketing in Japan.) 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.
7. In principle, duplicate descriptions in two or more sections should be avoided. However, this does not apply when precautions are listed in

multiple sections to prevent the occurrence of serious adverse reactions or defects. In such cases, the precautions to be described should be stated briefly in the "1. WARNINGS" and "2. CONTRAINDICATIONS" sections, and the section number to be referenced should be written following the precautions, such as "See 1.1.1," and the specific details should be described in the referenced section. If there are no or only insufficient data for an additional description, the description may be comprehensive rather than quantitative (e.g., cautiously, periodically, frequently, and as appropriate).

8. In principle, the contents to be described in the PRECAUTIONS should be those sections necessary for the use of a regenerative medical product within the scope of the approved "INDICATIONS OR PERFORMANCE" or "DOSAGE AND ADMINISTRATION OR METHODS OF USE." However, precautions that are deemed particularly necessary, such as serious adverse reactions or defects (In this notice, "defects" refers to "defects of a regenerative medical product" and is hereinafter simply referred to as "defects."), should be stated, even if they are descriptions concerning the use outside the scope of the approved "INDICATIONS OR PEFORMANCE" or "DOSAGE AND ADMINISTRATION OR METHODS OF USE." In selecting these sections, domestic and foreign information collected extensively should be evaluated and presented. In addition, precautions regarding infectious diseases caused by regenerative medical products should be described in the same manner as for adverse reactions.
9. When describing each section of "(16) PHARMACOKINETICS, " "(17) CLINICAL STUDIES," "(18) PRINCIPLE/MECHANISM," and "(19) STORAGE METHOD AND SHELF LIFE, etc.," an accurate description based on scientific and highly credible clinical studies and 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 data being exceptional shall be avoided.
10. When describing major sections, such as headings, methods such as using Gothic font or increasing the font size shall be devised to secure visibility.
11. 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.)
12. When describing each section from "(1) WARNINGS" to "(24) MARKETING AUTHORIZATION HOLDER, etc.," consideration shall be given to visibility, such as using a font size of around 8 points, in principle, unless otherwise specified.
13. 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."

14. For products for which "Guidelines for Promotion of Optimal Use" have been developed, "Product subject to Guidelines for Promotion of Optimal Use" should be indicated on the right side or below the brand name. If a part of the indications or performance are covered by the guideline, it should be described as "a product covered by the Guidelines for the Promotion of Optimal Use (partially)," and the indications or performance covered shall be annotated and clearly indicated.

II. Points to Consider for Each Section

A. Date of Preparation or Revision (year/month)

1) The dates of preparation or revision (year/month) followed by the version number in parentheses shall be included in the upper-left corner of the electronic package insert (hereinafter referred to as e-PI).
2) Revisions shall be made in the following manner when sections that will have a major effect on the use of the regenerative medical products are revised.
   i. 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 indicated.
   ii. For the revised part of description, for example, add "*" ahead of the section 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.
   iii. In the case of revision due to the release of reexamination results or re-evaluation results, a publication of the review results related to application for approval made again after a conditional and time-limited approval, or changes in the indications, dosage and administration, the method of use, such facts shall be stated in parentheses following the date of revision (year/month) "Reexamination Results" or "Re-evaluation Results," “Review

Results of Application after Conditional and Time-Limited Approval," "Change in the Indications," "Change in the Dosage," "Change in the Administration," or "Change in the Method of Use," respectively, following the version number.

B. Approval Number, etc.
   1) In principle, it shall be described on the right side of the brand name.
   2) When indicating the date of initial marketing, the heading for the date of initial marketing in Japan (year/month) shall be shortened to “Initial Marketing” and shall be written followed by the “Approval Number.”

C. 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). The classification shall be based on appended Table 2 (related to Article 1-2) of the Order for Enforcement of the Act on Quality, Efficacy and Safety Assurance of Pharmaceuticals, Medical Devices, etc. (Cabinet Order No. 11 of 1961). (However, the higher classifications of "human cell processed products," "animal cell processed products" and "gene therapeutic products" are not required to be listed.)
   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 e-PI 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 circled 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 circled in red.

D. 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.

1. WARNINGS

1) Information shall be written in red, including the heading, and enclosed within a red box.
2) WARNINGS should be written when fatal or extremely serious and irreversible adverse reactions occur even if the drug is used appropriately, or when the defects may occur and result in extremely serious adverse health effects and special attention is required.
3) For sections included in WARNINGS, the rationale or reason for setting the warning should be stated as necessary.
4) Any special precautions or emergency measures for adverse reactions or defects that occurred during use should be briefly described.
5) If standards for the facility or healthcare professionals used, etc., are required in the approval conditions, such fact shall be stated.
6) 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 spanning column ahead of the section "1. WARNINGS."

The specific expression shall be in accordance with Addendum 1.

i. 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.

ii. Safety measures to prevent transmission of infections are taken (describe specific safety measures in the section such as "IMPORTANT PRECAUTIONS" of "PRECAUTIONS").

iii. The risk of transmission of infections cannot be completely eliminated.

2. CONTRAINDICATIONS

1) Information including the heading shall be enclosed within a red box; however, the text shall not be written in red.
2) Patients to whom the product should not be administered shall be listed in view of their symptoms, underlying disease, complications, past history, family history, physical constitution, etc. Different patient groups shall be listed in a separate section if the patients have different reasons for contraindication.
3) For sections other than hypersensitivity that are created in the section of “CONTRAINDICATIONS,” the basis and the reason for setting should be described as necessary.
4) In principle, it must be consistent with the approved "INDICATIONS OR PERFORMANCE" to avoid misleading users.

3. SHAPE, STRUCTURE, INGREDIENTS, QUANTITY OR NATURE

1) 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. (They can be omitted for a product with a single component simply filled in a container.)
2) In addition to the main component to be used for the patient, for sub-components, such as machinery/equipment, etc. that directly come into contact with 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.
3) 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. 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.

i. For 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.

ii. 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.

iii. 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).

iv. 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).

4. INDICATIONS OR PERFORMANCE

For products listed as "Product with (partially) conditional and time-limited approval" in "Category and Nonproprietary Name, etc.,” indications or performances to be covered should be clearly indicated with annotations.

5. PRECAUTIONS CONCERNING INDICATIONS OR PERFORMANCE

1) When there are precautions related to indications or performance for

patients to whom the product should be used to prevent serious defects or adverse events, they shall be described by clearly separating them from the approved contents.

2) Precautions for clarifying the scope of indications approved, such as tests and diagnostic criteria necessary for patient selection, shall be included in this section.

6. DOSAGE AND ADMINISTRATION OR METHODS OF USE

It is desirable to add a graphical explanation as necessary.

7. PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION OR METHODS OF USE

In order to prevent serious defects or adverse events, when there are precautions for use related to dosage and administration or methods of use, and number, period, etc. of use, they shall be described 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 only in the section of Contraindications.

8. IMPORTANT PRECAUTIONS

1) In order to prevent serious defects or adverse events, when there are precautions for use related to dosage and administration or methods of use, indications or performance, period of use, selection of patients to whom the product should be used, tests to be performed, they should be specifically described.

2) 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 Addendum 1 or 2. Other basic precautions specific to the product shall be described in this section.

9. PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS

Precautions shall be included when special caution is required in determining applicability, dosage and administration or method of use, etc., or when laboratory tests and close observation of the patients are required, because the patients are at higher risk than other patients for the adverse

reactions or defects as described in i. through vii. below, judging from the patient's symptoms, primary disease, complications, medical history, family history, constitution, etc. The following cases are considered to be more hazardous than other patients. The reasons for the settings should be stated briefly as necessary (excluding hypersensitivity).

i. Cases in which adverse reactions or defects occur earlier
ii. When the incidence of adverse reactions or defects is high
iii. When more serious adverse reactions or defects occur
iv. When irreversible adverse reactions or defects occur
v. When adverse reactions or defects occur as a result of accumulation or long-term use
vi. When drug resistance changes
vii. Others

9.1 Patients with Complication or History of Diseases, etc.

It shall be described by adding an appropriate section, “9.1.1 Patients with XX,” according to complications, past history, family history, genetic predispositions, and other relevant factors.

9.2 Patients with Renal Impairment

Specific parameters for renal Impairment such as creatinine clearance and estimated glomerular filtration rate (eGFR) shall be described for the severity of renal impairment to the extent possible. If risks are assumed but there are no sufficient data on them because the applicable patients were excluded from clinical studies, such a fact shall be stated.

9.3 Patients with Hepatic Impairment

Specific parameters for hepatic impairment such as Child-Pugh classification shall be described for the severity of hepatic impairment to the extent possible. If risks are assumed but there are no sufficient data on them because the applicable patients were excluded from clinical studies, such a fact shall be stated.

9.5 Pregnant Women

1) Necessary precautions should be described in cases where more specific precautions are necessary compared to those for other patients or information on proper use is available, if it is possible that the product be used in pregnant or parturient patients taking into account its dosage and administration or methods of use and indication or performance.

2) Necessary matters based on data from non-clinical studies, clinical use experience, epidemiological surveys, or other relevant sources. If risks are assumed but there are no sufficient data on them because the applicable patients were excluded from clinical studies, such a fact shall be stated.
3) The following information should be included in particular.
   Information on the cases where defects, etc. are expected to occur due to the structural characteristics of pregnant or parturient women.

9.6 Breastfeeding Women

1) If it is possible that the product be used in breastfeeding women taking into account its dosage and administration or methods of use and indication or performance, and if more specific precautions are necessary compared to those for other patients or information on proper use is available, necessary precautions should be described.
2) If data from non-clinical studies, clinical use experience, epidemiological surveys, or other relevant sources are clinically beneficial, they shall be provided as information on appropriate use. If risks are assumed but there are no sufficient data on them because the applicable patients were excluded from clinical studies, such a fact shall be stated.
3) The following information should be included in particular.
   Information on the case where defects, etc. are expected to occur due to the structural characteristics of breastfeeding women.

9.7 Pediatric Use

1) Because of its dosage and administration or methods of use, indications or performance, it may be used in pediatrics etc. and if special caution is needed compared to other patients, or if there is information on proper use, the necessary precautions should be noted.
2) If data from non-clinical studies, clinical use experience, epidemiological surveys, or other relevant sources are clinically beneficial, they shall be provided as information on appropriate use. If risks are assumed but there are no sufficient data on them because the applicable patients were excluded from clinical studies, such a fact shall be stated.
3) The following information should be included in particular.
   Information on metabolic differences from adults (e.g., delayed disappearance from the blood due to undeveloped excretory functions)
   Information on potential defects in regenerative medical products due

to the unique structural characteristics of pediatrics etc.

4) The approximate age range of neonates, babies, infants, or children is described below. However, if the specific age is clear, “less than X years old,” “X years old or older, less than X years old” shall also be indicated. It is also acceptable to use age categories other than these:
   i. Neonates are aged under 4 weeks.
   ii. Babies are aged 4 weeks or older and under 1 year.
   iii. Infants are aged 1 year or older and under 7 years.
   iv. Children are aged 7 years or older and under 15 years.

9.8 Geriatric Use

1) Elderly people often have impaired physiological functions such as renal and hepatic functions, and there is a risk of increased risk in the use of regenerative medical products. In general, sufficient caution should always be exercised when applying regenerative medical products. If a regenerative medicine product is likely to be used in elderly patients due to its dosage and administration or methods of use, Indications or Performance, and if special precautions need to be taken in elderly patients compared to other patients, a section entitled "9.8 Geriatric Use" should be established to provide necessary precautions.
2) When describing information on Geriatric Use, the approximate age of the elderly shall be defined as 65 years or older, and, as necessary, information on the age group of 75 years or older shall also be included. However, if the specific age is clear, “X years old or older” shall also be indicated. It is also acceptable to use age groups other than these.
3) Contents of description
   i. If clinical trials, post-marketing surveillance or, if possible, Specific data such as pharmacokinetics suggest a problem when applied to Geriatric Use, briefly describe the details.
   ii. If risks are assumed but there are no sufficient data on them because the applicable patients were excluded from clinical studies such as fact shall be stated.
4) Specific description
   Regarding the specific descriptive expressions in (3) above, the characteristics of the relevant regenerative medical product, characteristics of the elderly, problems that may occur when the relevant regenerative medical product is applied to the elderly, and necessary precautions and treatments should be described in a concise and appropriate manner.

10. INTERACTIONS

1) Describe the information separately for Contraindications for Concomitant Use (Concomitant use is prohibited.) and Precautions for Concomitant Use (Concomitant use should be with caution.) depending on the contents as an outline of measures. The Section “10. Contraindications for Concomitant Use (Concomitant use is prohibited.) ” shall be written in a table with a red frame, but the text shall not be written in red.
2) The description format should be as clear as possible in a table format, etc. In some cases, it may be acceptable to use a descriptive format for the Precautions for Concomitant Use

Contraindications for Concomitant Use (Concomitant use is prohibited.)

Name of drug, etc.	Clinical Symptoms/ Measures	Mechanisms/ Risk Factors
(Nonproprietary Name・Brand Name)		

Precautions for Concomitant Use (Concomitant use should be with caution.)

Name of drug, etc.	Clinical Symptoms/ Measures	Mechanisms/ Risk Factors
(Nonproprietary Name)		

11. DEFECTS/ADVERSE REACTIONS

1) Among the health damages to the patient, those for which a causal relationship with the use of the regenerative medical product cannot be denied should be listed as side effects, and defects of the regenerative medical product should be listed as a defect, list each of these as a subsection.
2) The frequency of occurrence of adverse events/defects should be written based on the results of studies in which the number of cases is clear. In principle, the incidence shall be indicated as a percentage to one decimal place on the basis of the results of pooled clinical studies to investigate efficacy and safety of the regenerative medical products within the scope of approved indications and dosage and administration. If the incidence is less than 0.1%, such a fact shall be stated. In cases in which adverse reactions were accumulated from spontaneous reports

and Post-marketing Surveillance, etc. and the frequency is unknown, “frequency unknown” shall be added. However, only in cases where clinical study data are quite limited and it is particularly useful to describe the frequency of adverse reactions based on post-marketing surveillance, etc., the frequency shall be indicated by specifying the sources of references.

3) The following points should be noted when describing “Clinically Significant Adverse Reactions” and “Clinically significant Defects.”
    i. Sections that require special attention for the relevant regenerative medical product should be described.
    ii. When the mechanism of occurrence of adverse reactions and defects, the length of time before the adverse reactions and defects occur, specific preventive measures, and treatment methods, etc. are known, it is desirable to provide specific descriptions in parentheses, if necessary.
    iii. If there are early symptoms (including abnormal laboratory findings) and it is known that the progression of symptoms can be prevented by taking measures such as discontinuing use at the time the condition is recognized, the early symptoms should be described.
    iv. Clinically Significant Adverse Reactions/Defects known only in foreign countries should, in principle, be described in accordance with the adverse reactions/defects in Japan.
    v. Clinically Significant Adverse Reactions/Defects known to be caused by the same or similar products, etc. should be described in this section as necessary.

4) The following points should be noted when describing "Other Adverse Reactions" and "Other Defects."
    i. Adverse Reactions and Defects other than "Clinically significant Adverse Reactions" and " Clinically Significant Defects" should be classified by the site of occurrence, purpose of use, mechanism of action or mechanism of pathogenesis, etc., and should be described in an easy-to-understand manner by setting the frequency of occurrence in a table format.
    ii. Other Adverse Reactions/Defects known only in foreign countries should, in principle, be described in accordance with the adverse reactions/defects in Japan.

12. INFLUENCE ON LABORATORY TESTS

When the use of the Regenerative Medical Product causes apparent changes in laboratory data, and if it is not clearly linked to organic or functional disorders shall be described. (If a relationship with organic or functional disorders cannot be ruled out, describe this in the section “11. ADVERSE REACTIONS・DEFECTS.”)

13. OVERDOSE

Any examples of overdose should be described.

14. PRECAUTIONS CONCERNING USE

1) “Precautions Concerning Use” shall include precautions when preparing the product. The use of protectors (such as eyeglasses, gloves, and a mask) by persons preparing the regenerative medical product for avoiding exposure shall be described in this section.
2) “Precautions Concerning Administration” shall include precautions for the route of administration, injection rate, site of administration, and other relevant matters.

15. OTHER PRECAUTIONS

1) Even if an evaluation has not been established on data such as literature and reports, important information shall be accurately summarized by stating the phrase that “It has been reported that…”
2) Necessary precautions that do not fall under any of the previous sections should be described in this section (For example, descriptions regarding safety concerns in humans observed in Nonclinical Studies, etc.). In addition, when determining whether the description falls under this section, consider whether it is lethal, serious, and manageable.

17. CLINICAL STUDIES

17.1 Clinical Studies for Efficacy and Safety

1) The results of clinical studies used at the time of the approval application, or materials evaluated as substitutes for them, shall be described.
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. Safety results should be described based on adverse reactions, adverse events, or defects, and should be clearly stated as to which

results they are.

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.

17.2 Post-marketing Surveillance, etc.

The results of studies appropriately planned and implemented using a medical information database shall be described by clearly specifying the source of the quotation.

19. STRAGE 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.) shall be described.
3) Other precautions to confirm the quality before the use of the regenerative medical product shall be described if applicable.

20. PRECAUTIONS FOR HANDLING

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 Addendum 1.

21. 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.

22. REFERENCES

1) Literature for key data supporting the description of each section shall be cited in this section as references. It is desirable to preferentially describe literature supporting the description of clinical studies (results of controlled studies, adverse reactions, etc.).
2) For the relevant parts citing the contents of literature described as references, the reference number shall be given so that users can find the literature.
3) The main literature should be listed in Vancouver format (author name, journal name, publication year, volume number, first page - last page).
4) If in-house documents are cited, the specific content of the literature should be clearly described as much as possible so that users can easily request references. If a summary of approval application materials has been published, the relevant approval date and document number should also be included.
5) Literature suggesting "indications or performance" outside the scope of the application of the regenerative medical product shall not be described.

24. MARKETING AUTHORIZATION HOLDER, etc.

If the names of the distributor, licenser company, etc. are indicated, they shall be mentioned after the marketing authorization holder.

Addendum 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 an 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 an 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 (3)). The details of infection tests, details of inactivation treatment, limitations of safety measures, etc. shall be described in appropriate sections, such as "Precautions."

Example of a description for an 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. In addition, efforts shall be made to obtain their consent before using this regenerative medical product.

For autologous cell processed products, the following should be included in addition to the above

Explain to the patient in advance that the product may not be provided for reasons such as failure of the product to meet specifications.

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.

Addendum 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.

For autologous cell processed products, the following should be included in addition to the above

Explain to the patient in advance that the product may not be provided for reasons such as failure of the product to meet specification.