(6) That at the proper stage of manufacturing processes, the inspection and testing important for the quality control and impracticable in the product shall be performed.

(7) That all the articles, which have been contaminated by microorganisms, etc. (limited to those contaminated during the inspection and testing), shall be disposed of so as not to cause hazards to the public health and hygiene.

(8) That records on the use of cell strains for inspection and testing shall be prepared for the following matters, and the records shall be retained:

A. Name of cell strain and number given to each container;

B. Date of being transferred, and the name and address of a person who has transferred (in case of a corporation, name and address);

C. Biological properties and date of testing; and

D. Status of subculture.

(9) That records on the results of inspection and testing shall be prepared for each lot of products to be manufactured, and the records thereof shall be retained.

(10) That inspection and testing of donor animals at the time of or after their receipt and other necessary duties shall be performed by the manufacturers, etc. themselves or by a person designated beforehand according to the contents of the duties.

(11) That records on the duties specified in the preceding item shall be prepared and retained.

(12) Other duties necessary for quality control.

3. When the procedures to evaluate conformity with the standards for manufacturing control and quality control in an exporting country are found to be equivalent to those in Japan, inspection and testing (excluding visual inspection) specified in Item (2) of the preceding paragraph may be substituted for confirmation of records of the inspection and testing conducted by the foreign manufacturers of regenerative medicine products in an exporting country. In such a case, the manufacturers shall have the Quality Department properly implement the following duties:

(1) To periodically check that the products, etc. have been manufactured in accordance with the appropriate manufacturing procedures, etc.

(2) To periodically verify that the manufacturing sites of the foreign manufacturers of regenerative medicine products meet the standards for manufacturing control and quality control in that country.

(3) To prepare and retain records of confirmation in the preceding two items.

(4) To check the records of inspection and testing on the concerned product carried out by the foreign manufacturers of regenerative medicine products, and to prepare and retain the records of the confirmation.

4. Records on products specified in the preceding three paragraphs shall be retained so as to appropriately confirm a series of records from biological-origin raw materials for regenerative medicine products provided in manufacturing to a product manufactured with the biological-origin raw materials for regenerative medicine products.

5. The manufacturers, etc. shall have the Quality Department verify by lot the results of confirmation on manufacturing control reported by the Manufacturing Department pursuant to the provision of Paragraph 1, Item (8) of the preceding article in accordance with the operating procedures.

(Control of release from the manufacturing site)

Article 13 The manufacturers, etc. shall have the Quality Department implement duties to properly evaluate the results of manufacturing control and quality control, and determine whether or not the product can be released from the manufacturing site in accordance with the operating procedures.

2. Persons who carry out the duties set forth in the preceding paragraph shall have an ability to properly and smoothly perform the said duties.
3. The manufacturers, etc. shall make efforts for the effective performance of the duties assigned to the persons who implement the duties set forth in Paragraph 1.
4. The manufacturers, etc. shall not release the product from the manufacturing site until the decision set forth in Paragraph 1 is properly made.

(Validation or verification)

Article 14 The manufacturers, etc. shall have a person, designated beforehand, perform the following duties in accordance with the operating procedures:

(1) Validation shall be implemented in the following cases, provided, however, that if validation cannot be carried out due to compelling reasons, verification shall be conducted:
   A. When the manufacturing of a new product is started at the manufacturing site;
   B. When there are changes in the manufacturing procedures, etc. that may significantly affect the quality of the product; and
   C. Other cases where it is found to be necessary for properly implementing the manufacturing control and quality control of the product.

(2) The plan for and results of validation or verification shall be reported in writing to the Quality Department.

2. The manufacturers, etc. shall take required measures when it is found necessary to improve manufacturing control or quality control based on the results of the validation or verification set forth in Item (1) of the preceding paragraph, as well as prepare and retain the records of the said measures.

(Review of product quality)

Article 15 The manufacturers, etc. shall have a person, designated beforehand, perform the following duties in accordance with the operating procedures:

(1) That a review on the quality of products shall be implemented periodically or as necessary for the purpose of validating the consistency of manufacturing processes and the validity of the specifications of the products, etc.

(2) That the results of the review set forth in the preceding item shall be reported in writing to the Quality Department.

(3) That the report set forth in the preceding item shall be confirmed by the Quality Department.

2. The manufacturers, etc. shall have the Quality Department prepare and retain the records of the confirmation set forth in Item (3) of the preceding paragraph in accordance with the operating procedures and properly report them in writing to the Manufacturing Manager.
3. The manufacturers, etc. shall take required measures when it is found necessary to improve manufacturing control or quality control, or to implement validation or verification based on the results of the review set forth in Paragraph 1, Item (1), as well as prepare and retain the records of the said measures.

(Change control)

Article 16 When changes in the manufacturing procedures, etc. which may affect the quality of the product, are to be made, the manufacturers, etc. shall have a person, designated beforehand, implement the following duties in accordance with the operating procedures:

(1) To evaluate the effect of the said changes on the quality of products, obtain approval of the Quality Department for the changes based on the results of the evaluation, and prepare and retain the records thereof.

(2) When making the changes upon approval of the Quality Department pursuant to the provision of the preceding item, to revise relevant documents, give training to personnel and take other required measures.

(Deviation control)

Article 17 When there are deviations from the manufacturing procedures, etc. (hereinafter simply referred to as "deviations"), the manufacturers, etc. shall have a person, designated beforehand, implement the following duties in accordance with the operating procedures:

(1) That the details of deviations shall be recorded.

(2) That the following duties shall be performed when major deviations occurred:

A. To evaluate the effect of deviations on the quality of products, and take required measures;

B. To prepare and retain the records on the results of the evaluation and the measures specified in Item A, and report them in writing to the Quality Department; and

C. To have confirmation of the Quality Department on the results of the evaluation and the measures reported pursuant to the provision of Item B.

2. The manufacturers, etc. shall have the Quality Department prepare and retain the records on the confirmation pursuant to the provision of Item (2), C of the preceding paragraph in accordance with the operating procedures and properly report in writing with the records set forth in Item (2), B to the Manufacturing Manager.

(Handling of quality information and quality defects)

Article 18 When receiving information on the quality and other relevant matters of products (hereinafter referred to as the "quality information"), the manufacturers, etc. shall have a person, designated beforehand, implement the following duties in accordance with the operating procedures excluding the

case where matters concerning the quality information are clearly not attributable to the manufacturing site:

(1) To investigate into the cause of the matter concerning the quality information, and take required measures when improvement in manufacturing control or quality control is needed.

(2) To prepare and retain records describing the details of the quality information, the results of the investigation into the cause and corrective measures taken, and promptly report them in writing to the Quality Department.

(3) To have confirmation of the Quality Department for the report set forth in the preceding item.

2. When quality defects or suspected quality defects are identified as a result of the confirmation set forth in Item (3) of the preceding paragraph, the manufacturers, etc. shall have the Quality Department report the said matter in writing to the Manufacturing Manager in accordance with the operating procedures.

(Recall action)

Article 19 When recall is implemented because of reasons on the quality, etc. of products, the manufacturers, etc. shall have a person, designated beforehand, implement the following duties in accordance with the operating procedures:

(1) If the recalled products are stored, to store them by separation for a certain period of time and then properly dispose the products.

(2) To prepare and retain records on a recall action describing the details of the recall, and report them in writing to the Quality Department and Manufacturing Manager, provided, however, that this provision shall not apply to the case where the reason for implementing the recall is revealed to be not attributable to the concerned manufacturing site.

(Self-inspections)

Article 20 The manufacturers, etc. shall have a person, designated beforehand, implement the following duties in accordance with the operating procedures:

(1) To perform the periodic self-inspections on the manufacturing control and quality control of products at the manufacturing site.

(2) To report the results of the self-inspections in writing to the Manufacturing Manager.

(3) To prepare and retain records of the self-inspection results.

2 The manufacturers, etc. shall take required measures when it is found necessary to improve manufacturing control or quality control based on the results of the self-inspections set forth in Item (1) of the preceding paragraph, as well as prepare and retain the records of the said measures.

(Training)

Article 21 The manufacturers, etc. shall have a person, designated beforehand, implement the following duties in accordance with the operating procedures:

(1) To systematically implement necessary training on manufacturing control and quality control for personnel engaged in the manufacturing and quality control duties.

(2) To provide personnel engaged in manufacturing or inspection and testing with training on hygienic control, microbiology, medicine, veterinary medicine and other necessary matters for the manufacturing of products.

(3) To give training on measures necessary for preventing contamination by microorganisms, etc. to personnel who are engaged in duties in the controlled clean area, aseptic operation area, etc. and duties related to the culture or other processing of human or animal cells or microorganisms, etc. used for the manufacturing of products.

(4) To report the status of implementation of training in writing to the Manufacturing Manager.

(5) To prepare and retain records on the implementation of training.

(Document and record control)

Article 22 The manufacturers, etc. shall have a person, designated beforehand, implement the following duties concerning documents and records specified in this Ordinance in accordance with the operating procedures:

(1) When preparing or revising documents, to implement approval, distribution, retention and other relevant matters in accordance with the operating procedures.

(2) When preparing or revising the operating procedures, to record its date in the operating procedures, and to keep a history of the previous revisions.

(3) To retain documents and records specified in this Ordinance for the following periods (5 years for records on training) from the date of preparation (date when documents are no longer used for the operating procedures):

A. A period of the expiry date plus 30 years for specified regenerative medicine products; and

B. A period of the expiry date plus 10 years for regenerative medicine products (excluding those mentioned in Item A).

(Exceptions for retention of records)

Article 23 Notwithstanding the provisions of the preceding article, the manufacturers, etc. shall have a person, designated beforehand, retain records specified in the preceding article for regenerative medicine products designated by the Minister of Health, Labour and Welfare, for the period stipulated by the Minister of Health, Labour and Welfare, provided, however, that this provision shall not apply to the case where a contract has been closed between the manufacturers, etc. and raw materials collecting firms, etc., and these records shall be appropriately retained for the concerned period by the raw materials collecting firms, etc.

Supplementary Provisions

(Date of enforcement)

Article 1 This Ordinance shall come into effect on the date of enforcement (November 25, 2014) of the Law for Partial Revision of the Pharmaceutical Affairs Law and Other Relevant Laws and Regulations (Law No. 84 in 2013).

(Partial Revision of the Ministerial Ordinance concerning Rearrangement of Relevant Ministerial Ordinances in Association with the Enforcement of the Law for Partial Revision of the Pharmaceutical Affairs Law and Other Relevant Laws and Regulations, and Cabinet Order concerning Rearrangement of Relevant Cabinet Orders and Interim Measures in Association with the Enforcement of the Law for Partial Revision of the Pharmaceutical Affairs Law and Other Relevant Laws and Regulations)

Article 2 The Ministerial Ordinance concerning Rearrangement of Relevant Ministerial Ordinances in Association with the Enforcement of the Law for Partial Revision of the Pharmaceutical Affairs Law and Other Relevant Laws and Regulations, and Cabinet Order concerning Rearrangement of Relevant Cabinet Orders and Interim Measures in Association with the Enforcement of the Law for Partial Revision of the Pharmaceutical Affairs Law and Other Relevant Laws and Regulations (Ordinance No. 87 of the Ministry of Health, Labour and Welfare in 2014) is partially revised as follows:

In Article 37, paragraphs on the Ministerial Ordinance on Good Manufacturing Practice (GMP) for Regenerative Medicine Products (Ordinance No. Ministry of Health, Labour and Welfare in 2014) among revised provisions, which are added to Attached Table 1-1 as mentioned below, are deleted, and the belowmentioned table is added after the paragraph on the Ministerial Ordinance on Good Postmarketing Study Practice (GPSP) for Regenerative Medicine Products (Ordinance No. 90 of the Ministry of Health, Labour and Welfare in 2014).

Ministerial Ordinance on Good Manufacturing Practice (GMP) for Regenerative Medicine Products (Ordinance No. Ministry of Health, Labour and Welfare in 2014)	Retention of the product master formula pursuant to the provisions of Article 8
	Retention of the sanitation control standard code pursuant to the provisions of Article 9, Paragraph 1
	Retention of the manufacturing control standard code pursuant to the provisions of Article 9, Paragraph 2
	Retention of the quality control standard code pursuant to the provisions of Article 9, Paragraph 3
	Retention of the Procedures pursuant to the provisions of Article 9, Paragraph 4
	Installation of the operating procedures pursuant to the provisions of Article 9, Paragraph 5
	Retention of the manufacturing order pursuant to the provisions of Article 11, Item (1)
	Retention of the documents pursuant to the provisions of Article 22, Item (1)
	Retention of the documents pursuant to the provisions of Article 22, Item (3)

Standards for Biological Materials

Established on May 20, 2003 (MHLW Notification No. 210)
Established on March 30, 2004 (MHLW Notification No. 157)
Established on July 5, 2004 (MHLW Notification No. 262)
Established on March 31, 2005 (MHLW Notification No. 177)
Established on September 28, 2007 (MHLW Notification No. 310)
Established on July 1, 2009 (MHLW Notification No. 343)
Established on September 26, 2014 (MHLW Notification No. 375)

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General Notices

(Standards for Biological Materials Chapter 1)

1 The Standards stipulate standards for necessary measures, which should be taken when using materials (including those utilized during manufacturing processes such as additives and culture media) derived from humans and other organisms (excluding plants) for manufacturing of drugs, quasi-drugs, cosmetics, medical devices and regenerative medicine products (hereinafter referred to as "drugs, etc.") for the purpose of ensuring the quality, efficacy and safety of drugs, etc.

2 The Standards do not apply to materials used for *in vitro* diagnostics or products not to be directly utilized in the human body, or microorganisms or viruses employed for the manufacturing of vaccines.

3 The term "raw materials" refers to materials employed for the manufacturing of drugs, etc. or those which are the origins of materials. The term "materials" refers to materials, or ingredients or their raw materials.

4 The term "source plasma" refers to plasma, which is isolated from materials, as necessary, using an appropriate method, and a group of individual isolated plasmas or those mixed with all or some of individual isolated plasmas for the manufacturing of plasma fraction products.

5 The term "donor" refers to an individual providing his or her cells or tissues as the materials of drugs, etc. (excluding materials derived from the human body with brain death as specified in Article 6, Paragraph 2 of the Law on Organ Transplantation (Law No. 104 in 1997)).

6 The term "donor animal" refers to an animal other than a human providing its cells or tissues as the materials of drugs, etc.

7 The term "donor screening" refers to performing a diagnosis based on interviews and tests of donors, or inspection/testing and breeding/keeping of donor animals to decide whether or not such donors or donor animals are fully eligible to provide their cells or tissues as the materials of drugs, etc.

8 The term "window period" refers to an early phase of infection during which bacteria, fungi, viruses, etc. or their antigens, antibodies, genes, etc. are not detectable.

9 For drugs, etc. which have been demonstrated to have validity equivalent to or higher than that specified in the Standards in terms of their quality and safety, and for which such a fact is described in approval certificates issued at the time of marketing approval, the concerned provisions of the Standards are not applicable.

10 When drugs, etc. approved for marketing are properly used as the materials of other drugs, etc., drugs, etc. approved for the marketing are deemed as materials conforming with the Standards.

General Rules for Transfusion Blood Products

(Standards for Biological Materials Chapter 2 "General Rules for Blood Products" Section 1)

(1) Providers of blood to be used for transfusion blood products (hereinafter referred to as "blood donors" in the General Rules for Transfusion Blood Products) shall be individuals who are not suspected to be affected by diseases transmitted through blood based on interviews or other relevant means and fully eligible for providing blood to be the materials of transfusion blood products, provided, however, that this provision shall not apply to the case where bacteria, fungi, viruses, etc. transmitted through blood are confirmed to be inactivated or eliminated during the manufacturing processes, and such a

fact is described in approval certificates issued at the time of marketing approval for the concerned transfusion blood products.

(2) Blood shall be collected using any of the following blood collection methods:

A. Whole blood collection

A method to use a blood set to which an appropriate blood preservation fluid is injected and a blood collection needle is immediately set up, and then which is sealed and steam sterilized.

B. Collection of blood components

A method to collect only specific blood components such as plasma and platelet, and return components other than these that is carried out using the following procedures:

(A) A procedure to collect whole blood in accordance with the method set forth in Item A and then specific blood components using an appropriate method, and to return blood components other than these.

(B) A method to collect specific blood components as mixing blood with an appropriate blood preservation fluid and extracorporeally circulate it using an apparatus for collection of blood components.

(3) For the materials of transfusion blood products, excluding separately specified cases, any of the following items collected using the blood collection methods stipulated in Item (2) shall be utilized:

A. Blood collected through whole blood collection

B. Platelet-rich plasma collected through the collection of blood components

C. Plasma collected through the collection of blood components

(4) The materials of transfusion blood products shall be stored at 1°C to 10°C. However, in the case of manufacturing platelet preparations or isolating blood components, they may be stored at ordinary temperatures.

(5) Blood used as the materials of transfusion blood products shall be serologically tested by each blood transfusion collected from one blood donor for at least treponema pallidum, hepatitis B virus (HBV), hepatitis C virus (HCV), human immunodeficiency virus (HIV-1 and HIV-2) and human T-cell lymphotropic virus type I (HTLV-1). When the results of these tests revealed that the blood is ineligible, excluding materials specified in each article concerning drugs of the Minimum Requirements for Biological Products (Notification No. 155 of the Ministry of Health, Labour and Welfare in 2004), it shall not be used as a material of transfusion blood products.

(6) Blood used as the materials of transfusion blood products shall be tested by nucleic-acid amplification tests for at least HBV DNA, HCV RNA and HIV RNA. When the results of these tests detected HBV DNA, HCV RNA or HIV RNA in the blood, such blood shall not be utilized as a material of transfusion blood products.

(7) Blood used as the materials of transfusion blood products shall be tested for blood types, by each blood transfusion collected from one blood donor, using antibodies for determining ABO blood types and Rh blood grouping.

For ABO blood type testing, known types A and B erythrocytes shall be used, and the serum or plasma shall be also tested to determine a blood type. Also, anti-A antibodies for determining blood types or dried anti-A antibodies for determining blood types and anti-B antibodies for determining blood types or dried anti-B antibodies for determining blood types meeting the Minimum Requirements for Antibodies for Blood Typing (Notification No. 204 of the Ministry of Health and Welfare in 1994) shall be employed.

For Rh blood grouping, anti-D antibodies for determining blood types or mixed anti-D antibodies for determining blood types meeting the Minimum Requirements for Antibodies for Blood Typing shall be used, and D (Rho) positive or negative shall be assessed in accordance with a required method of use. If this test gives a negative result, an additional test shall be carried out using anti-human globulin antibodies (polyspecific antibodies) meeting the Minimum Requirements for Antibodies for Blood Typing.

(8) Records on the following matters shall be prepared and retained so that information necessary for ensuring the quality and safety of blood used as the materials of transfusion blood products can be verified:

A. Name of the place where blood is collected;
B. Date of blood collection;
C. Records on medical checkup of blood donor such as medical records;
D. Results of serological and nucleic-acid amplification tests;
E. Course of operations to collect the blood;
F. Number identifying the donor of the blood; and
G. In addition to those listed in Items A to F, matters necessary for ensuring the quality and safety of a transfusion blood product.

General Rules for Plasma Fraction Products

(Standards for Biological Materials Chapter 2 "General Rules for Blood Products" Section 2)

(1) Providers of blood to be used for plasma fraction products (hereinafter referred to as "blood donors" in the General Rules for Plasma Fraction Products) shall be individuals who are not suspected to be affected by diseases transmitted through blood based on interviews or other relevant means and fully eligible for providing blood to be the materials of plasma fraction products, provided, however that, this provision shall not

apply to the case where bacteria, fungi, viruses, etc. transmitted through blood are confirmed to be inactivated or eliminated during the manufacturing processes, and such a fact is described in approval certificates issued at the time of marketing approval for the concerned plasma fraction products.

(2) Blood shall be collected using the blood collection methods set forth in the Section 1, General Rules for Transfusion Blood Products, (2).

(3) For the materials of plasma fraction products, excluding separately specified cases, any of the following items collected using the blood collection methods stipulated in Item (2) shall be utilized:

A. Blood collected through whole blood collection

B. Platelet-rich plasma collected through the collection of blood components

C. Plasma collected through the collection of blood components

(4) When storing the materials of plasma fraction products, those falling into Item (3), A shall be stored at ≤ 10°C by avoiding their freezing, and those falling into Item (3), (B) or (C) shall be stored at ≤ 10°C.

(5) Blood used as the materials of plasma fraction products shall be serologically tested for at least hepatitis B virus (HBV), hepatitis C virus (HCV), and human immunodeficiency virus (HIV-1 and HIV-2). When the results of these tests revealed that the blood is ineligible, excluding materials specified in each article concerning drugs of the Minimum Requirements for Biological Products, it shall not be used as a material.

(6) Blood used as the source plasma of plasma fraction products shall be tested by nucleic-acid amplification tests for at least HBV DNA, HCV RNA and HIV RNA, provided, however, that this provision shall not apply to the case where nucleic-acid amplification tests revealed that no HBV DNA, HCV RNA or HIV RNA has been detected in the blood as the materials of source plasma. When the results of these tests detected HBV DNA, HCV RNA or HIV RNA in the plasma, such plasma shall not be utilized as source plasma.

(7) When storing source plasma, it shall be stored at ≤ 6°C.

(8) Records on the following matters shall be prepared and retained so that information necessary for ensuring the quality and safety of blood and source plasma used as the materials of plasma fraction products can be verified:

A. Name of the place where the material is collected;

B. Date of collection of the material;

C. Records on medical checkup of the donor of blood used for source plasma such as medical records;

D. Results of serological and nucleic-acid amplification tests;

E. Course of operations to collect the material and to produce source plasma;

F. Manufacturing numbers of material and source plasma;
G. Number identifying the donor of the blood used for source plasma; and
H. In addition to those listed in Items A to G, matters necessary for ensuring the quality and safety of a plasma fraction product.

Standards for Human Cell and Tissue Materials

(Standards for Biological Materials Chapter 3 "General Rules for Human-derived Materials" Section 1)

(1) Cells or tissues derived from humans used as materials (hereinafter referred to as "human cell and tissue materials") composing drugs, etc. (excluding blood products) shall be collected at establishments having personnel and facilities adequate for implementing hygienic control necessary for collection.

(2) When collecting human cell and tissue materials, the following measures shall be taken:
A. Measures necessary for preventing contamination by pathogenic microorganisms or other factors causing diseases during the process of collecting human cell and tissue materials.
B. It shall be confirmed that collected human cell and tissue materials are, as necessary, appropriately tested in the light of the latest evidence on infection and not contaminated by pathogenic microorganisms or other factors causing diseases.

(3) Donors shall meet all of the following requirements and be fully eligible for providing human cell and tissue materials, provided, however, that donor screening is not always required if the target users of drugs, etc. and the donors are the same individuals:
A. When collecting human cell and tissue materials, infection with bacteria, fungi, viruses, etc. shall be ruled out based on interviews, medical checkups and tests according to the purpose of their use.
B. Test items and test methods set forth in Item A are appropriate in the light of the latest evidence on infections.
C. Tests or control while taking account of a window period has been implemented; e.g., a retest is performed in a timely manner according to the test items and test methods set forth in Item A.
D. In addition to the matters set forth in Items A to C, interviews, medical checkups and tests shall be carried out for necessary diseases, as well as donors shall be determined to be eligible in consideration that they have or have not received transfusion or transplantation medicine.

(4) Persons who collect human cell and tissue materials shall confirm that the human cell and tissue materials fulfill the following requirements, and are appropriate to be used for drugs, etc.:

A. When collecting human cell and tissue materials from dead persons, honor shall be paid to them, an appropriate written explanation using as simple expressions as possible shall be given to their bereaved families concerning the usage of human cell and tissue materials and other necessary matters for collecting human cell and tissue materials, and written consent shall be obtained.

B. When receiving human cell and tissue materials, an appropriate written explanation, using as simple expressions as possible, on the following matters shall be given to donors, and written consent shall be obtained:

(A) Usage of human cell and tissue materials;

(B) Anticipated risks and disadvantages associated with the provision of human cell and tissue materials;

(C) That to become a donor is voluntary;

(D) Matters concerning withdrawal of consent;

(E) Refusal to provide human cell and tissue materials or withdrawal of consent for providing human cell and tissue materials shall not give any unfavorable treatment;

(F) Matters concerning expenses for providing human cell and tissue materials;

(G) Matters concerning compensation for health injury associated with the provision of human cell and tissue materials;

(H) Matters concerning the protection of personal information of donors;

(I) Matters concerning the attribution of patent rights, copy rights and other property rights or economic benefits related to drugs, etc. using human cell and tissue materials; and

(J) Other necessary matters according to the contents of drugs, etc. using human cell and tissue materials.

C. When receiving human cell and tissue materials, if consent is obtained from the representative of a donor, an appropriate written explanation, using as simple expressions as possible, on the following matters shall be given to the representative, and written consent shall be obtained:

(A) Usage of human cell and tissue materials;

(B) Anticipated risks and disadvantages associated with the provision of human cell and tissue materials;

(C) That to become a representative is voluntary;

(D) Matters concerning withdrawal of the consent of the representative;

(E) Refusal to provide the consent of the representative or withdrawal of the consent of the representative shall not give any unfavorable treatment;

(F) Matters concerning expenses for providing human cell and tissue materials;

(G) Matters concerning compensation for health injury associated with the provision of human cell and tissue materials;

(H) Matters concerning the protection of personal information of donors and representatives;

(I) Matters concerning the attribution of patent rights, copy rights and other property rights or economic benefits related to drugs, etc. using human cell and tissue materials; and

(J) Other necessary matters according to the contents of drugs, etc. using human cell and tissue materials.

D. When receiving human cell and tissue materials, if the consent of a representative is obtained, records on the consent of the representative and records on the relationship between the representative and a person providing human cell and tissue materials shall be prepared.

E. In the case where donors agree that human cell and tissue materials are to be used for drugs, etc., an opportunity for the concerned donors to be able to withdraw their consent shall be ensured during a period until the culture and other processing of the human cell and tissue materials are done.

F. In the case where human fertilized embryos are provided, after consent for the provision of human cell and tissue materials, the human cell and tissue materials shall be stored at medical institutions for at least 30 days without establishing human embryonic stem cells so that an opportunity for the donors to withdraw their consent is ensured.

G. When receiving human fertilized embryos, they shall be those meeting the following requirements:

(A) Of fertilized embryos prepared to be used for assisted reproduction technologies that are not planned to be used for the said purpose for the time being, those for which the donors' will is confirmed for the destruction of the fertilized embryos;

(B) Those which have been frozen and stored;

(C) Those within 14 days after fertilization excluding a period during which they are frozen and stored; and

(D) Those which have undergone processes necessary for properly establishing human embryonic stem cells.

H. Human cell and tissue materials shall be provided for free of charge, provided, however, that this provision shall not apply to those equivalent to transportation expenses and other actual expenses incurred in the provision of human cell and tissue materials.

I. When collecting human cell and tissue materials, the priority shall be given to the collection of human cell and tissue materials, and human cell and tissue materials shall not be those collected by changing medical procedures, surgery or other therapeutic policies.

(5) Records on the following matters shall be prepared and retained so that information necessary for ensuring the quality and safety of human cell and tissue materials can be verified:

A. Establishment where the human cell and tissue material is collected;

B. Date of collection of the human cell and tissue material;

C. Diagnostic result based on interviews, medical checkups and tests for donor screening and its status;

D. Course of operations to collect the human cell and tissue material;

E. The results of deliberations by the ethics committee;

F. Informed consent document and form;

G. Identification number of the donor; and

H. In addition to those listed in Items A to G, matters necessary for ensuring the quality and safety of drugs, etc.

Standards for Human Urine-derived Materials

(Standards for Biological Materials Chapter 3 "General Rules for Human-derived Materials" Section 2)

(1) The provisions of the Item (4), H of the Standards for Human Cell and Tissue Materials shall apply *mutatis mutandis* to human urine and pooled urine (referring to a mixture of urine collected from each provider or multiple providers; the same applies hereinafter) to be used as the materials of drugs, etc. (hereinafter referred to as "human urine").

(2) It shall be verified at an appropriate stage that human urine is properly tested for infection and not contaminated by pathogenic microorganisms, provided, however that, this provision shall not apply to the case where pathogenic microorganisms or other factors causing diseases are confirmed to be inactivated or eliminated during the manufacturing

processes, and such a fact is described in approval certificates issued at the time of marketing approval for the concerned products.

(3) Pooled urine shall be tested by nucleic-acid amplification tests for at least HBV DNA, HCV RNA and HIV RNA at an appropriate stage, provided, however, that this provision shall not apply to the case where urine, for which appropriate nucleic-acid amplification tests detected no HBV DNA, HCV RNA or HIV RNA, is used as a material.

(4) It shall be confirmed that bacteria, fungi, viruses, etc. are confirmed to be inactivated in or eliminated from human urine during the manufacturing processes, provided, however, that this provision shall not apply to the case where there is a rational reason for not performing such processing and such a fact is described in approval certificates issued at the time of marketing approval.

(5) Records on the following matters shall be prepared and retained so that information necessary for ensuring the quality and safety of human urine can be verified:

A. Name of the laboratory which prepared human urine;
B. Date of preparation of human urine;
C. Results of tests of human urine;
D. Processes of operations to prepare human urine;
E. Lot number of human urine; and
F. In addition to those listed in Items A to E, matters necessary for ensuring the quality and safety of drugs, etc.

Standards for Human-derived Materials

(Standards for Biological Materials Chapter 3 "General Rules for Human-derived Materials" Section 3)

(1) Cells or tissues (including cell strains and cells after completing culture for products produced through cell culture using a cell bank as the starting material), which are the origin of those derived from humans (excluding human cell and tissue materials, human urine and materials which are scientifically known to have no risk of infection with bacteria or viruses; hereinafter referred to as "human-derived materials") utilized as the materials of drugs, etc. (excluding blood products), shall be tested for viruses at an appropriate stage. If this test detects any extraneous virus, in principle, the said human-derived materials shall not be used for manufacturing drugs, etc., provided, however, that this provision shall not apply to the case where materials that are prepared using human-derived cell banks and have been established at the time of application of the Standards, and for which the said test has demonstrated the validity of using them as

materials being equivalent or higher in terms of quality and safety assurance, and such facts are described in approval certificates issued at the time of marketing approval.

(2) Providers of human-derived materials originated from human blood shall be individuals who are not suspected to be affected by diseases transmitted through blood based on interviews or other relevant means and fully eligible for providing blood to be the human-derived materials.

(3) Processes to inactivate or eliminate bacteria, fungi, viruses, etc. shall be performed for human-derived materials during the manufacturing processes, provided, however, that this provision shall not apply to the case where there is a rational reason for not performing such processing and such a fact is described in approval certificates issued at the time of marketing approval.

(4) Records on the following matters shall be prepared and retained so that information necessary for ensuring the quality and safety of human-derived materials can be verified:

A. Name of the laboratory which prepared human-derived materials;
B. Date of preparation of human-derived materials;
C. Results of tests of human-derived materials;
D. Lot numbers of human-derived materials; and
E. In addition to those listed in Items A to D, matters necessary for ensuring the quality and safety of the product.

Standards for Ruminant Animal-derived Materials

(Standards for Biological Materials Chapter 4 "General Rules for Animal-derived Materials" Section 1)

(1) The following sites shall not be used as materials derived from ruminant animals to be used as the materials of drugs, etc. (excluding materials manufactured using high-temperature and alkali treatment and those produced using other appropriate processing; hereinafter referred to as "ruminant animal-derived materials"):

A. Pituitary gland
B. Thymus
C. Dura mater
D. Trigeminal ganglion
E. Epiphysis
F. Spinal cord
G. Spinal bones

H. Placenta
I. Skull
J. Intestines
K. Brain
L. Cerebrospinal fluid
M. Dorsal root ganglion
N. Spleen
O. Adrenal gland
P. Tonsil
Q. Eyes
R. Lymph nodes

(2) The origin countries of ruminant animal-derived materials shall be countries where the World Organization for Animal Health considers that the risk of transmission of bovine spongiform encephalopathy pathogens in the countries can be ignored as well as the belowmentioned countries, provided, however, that this provision shall not apply to wool, milk, bones and skin-derived gelatin (including collagen) (hereinafter referred to as "low-risk materials") and injections manufactured through cell culture using ruminant animal-derived materials originated from Canada (hereinafter referred to as "materials produced in Canada") (limited to those using materials produced in Canada only for cell banks), other materials equivalent to these, vaccines (limited to oral vaccines) manufactured using materials produced in Canada, injections manufactured through the culture of microorganisms using materials produced in Canada (limited to those using materials produced in Canada only for seed culture), oral formulations, other materials equivalent to these and external formulations manufactured using materials produced in Canada:

A. El Salvador
B. Kenya
C. Costa Rica
D. Swaziland
E. Nigeria
F. Namibia
G. Nicaragua
H. New Caledonia
I. Pakistan
J. Vanuatu

K. Botswana

L. Mauritius

(3) Records on the following matters shall be prepared and retained so that information necessary for ensuring the quality and safety of ruminant animal-derived materials (excluding low-risk materials) can be verified:

A. Origin country;

B. Date of preparation of ruminant animal-derived materials;

C. Status of breeding or slaughter of ruminant animals that are the origin of ruminant animal-derived materials;

D. Course of processing and operations to prevent transmissible spongiform encephalopathy for ruminant animal-derived materials; and

E. Lot numbers of ruminant animal-derived materials.

(4) For drugs, quasi-drugs, medical devices and regenerative medicine products, when the therapeutic efficacy of using ruminant animal-derived materials outweighs risk and it is necessary for other reasons, and when ruminant animal-derived materials not meeting Item (1) or (2) are to be utilized for compelling reasons, such appropriateness shall be documented in approval certificates issued at the time of marketing approval.

(5) For cosmetics, when ruminant animal-derived materials not meeting Item (2) are to be utilized for compelling reasons, only those, which meet required conditions specified by the Director-General of the Pharmaceutical and Food Safety Bureau, Ministry of Heath, Labour and Welfare, may be used.

Standards for Animal Cell and Tissue Materials

(Standards for Biological Materials Chapter 4 "General Rules for Animal-derived Materials" Section 2)

(1) Cells or tissues derived from animals used as materials (hereinafter referred to as "animal cell and tissue materials") composing drugs, etc. shall be collected at establishments having personnel and facilities adequate for implementing hygienic control necessary for collection.

(2) When collecting animal cell and tissue materials, measures necessary for preventing contamination by pathogenic microorganisms or other factors causing diseases during the process of collection shall be taken.

(3) Donor animals of animal cell and tissue materials shall be confirmed to be fully eligible for providing animal cell and tissue materials, provided, however, that materials, which are

the origin of materials of drugs, etc. and produced through cell culture using cell banks with use experience and being analyzed for characteristics as the starting materials, are excluded.

(4) For the use of animal cell and tissue materials, it shall be confirmed that the risk of viral infection has been tested and other necessary matters have been implemented.

(5) Records on the following matters shall be prepared and retained so that information necessary for ensuring the quality and safety of animal cell and tissue materials can be verified, provided, however, that materials, which are the origin of materials of drugs, etc. and produced through cell culture using cell banks with use experience and being analyzed for characteristics as the starting materials, are excluded:

A. Establishment where the animal cell and tissue material is collected;
B. Date of collection of animal cell and tissue materials;
C. Status of acceptance of donor animals, and the status of inspection/ testing and breeding/ control;
D. Course of operations to collect the animal cell and tissue materials;
E. Lot numbers of animal cell and tissue materials; and
F. In addition to those listed in Items A to E, matters necessary for ensuring the quality and safety of the product.

Standards for Animal-derived Materials

(Standards for Biological Materials Chapter 4 "General Rules for Animal-derived Materials" Section 3)

(1) For materials derived from animals used as the materials of drugs, etc. (excluding animal cell and tissue materials, and materials which are scientifically known to have no risk of infection with bacteria, fungi, viruses, etc.; hereinafter referred to as "animal-derived materials"), excluding the case of deriving from healthy animals, it shall be confirmed that sterility is ensured, the risk of viral infection has been tested, and other necessary matters have been implemented.

(2) Products produced through cell culture using cell banks derived from animals and analyzed for characteristics as the starting materials shall be tested for viruses at an appropriate stage. If this test detects any extraneous virus, in principle, the said products shall not be used for manufacturing drugs, etc., provided, however, that this provision shall not apply to the case where materials that are produced using cell banks and have been established at the time of application of the Standards, and for which the said test has