(3) The operation regarding creating a manufacturing order indicated in Paragraph 1, Item 1 shall be conducted by a personnel with thorough knowledge of this operation who was designated to be the responsible person, and the responsibility, etc., of this personnel shall have been prescribed in the document prescribed in Article 7, Paragraph 4.

(4) "Instructions, precautions and other necessary matters during manufacturing processes" indicated in Paragraph 1, Item 1 shall be the following matters:

A. The commander and date of order.

B. Name, structure, property, appearance, and lot number or manufacturing number of the product.

C. Place of manufacturing and major buildings and facilities intended to be used (including necessary procedures, etc., for using in washing, assembly, inspection, sterilization, etc.).

D. List of raw materials and packaging and labeling materials intended to be used.

E. Details of the instruction or precaution in conducting operations in each manufacturing process (shall include confirmation items prior to initiation of operation; strength of the raw material or amount prepared and the sequence in which they are added; inactivation/elimination of microorganisms, etc.; time limit of the operation, taking into account the property of the cell or tissue; specification of the package and labeling; etc.).

F. Details of process control in each manufacturing process (including limits) (e.g., theoretical yield of the product (or standard yield, etc., if there is difficulty calculating theoretical yield)).

G. Instructions or precautions regarding material (if appropriate, attach a sample labeling material and a sample indicating the place for labeling).

H. Other necessary matters for manufacturing order.

(5) Provisions in Paragraph 1, Item 2 prescribes that operations in each manufacturing process within the manufacturing division is required to be conducted based on the manufacturing order.

(6) Manufacturing records: "Records on the manufacturing of products" indicated in Paragraph 1, Item 3 shall mean the so-called manufacturing records, and the following items shall be recorded in them:

A. Product name and lot number or manufacturing number

B. Name of manufacturing process, date of operation (and time, as necessary), and name of personnel conducting the operation

C. Raw material name, lot number or manufacturing number, special notes (information on the donor or donor animal), and strength or amount prepared

D. Material name, control number, and receipt/distribution

E. Yield on production and standard yield in each manufacturing process

F. Results of testing by the manufacturing division pertaining to process control and measures taken for disqualified results

G. Measures taken for disqualified results of testing conducted by the quality division

H. Confirmation results of whether each manufacturing process was conducted in accordance to the manufacturing order

I. Other measures taken during manufacturing operation

J. The person who took records and recording date

K. Necropsy findings in animals used in manufacturing or testing

L. Final expiration date or expiration date for use for products that are required to have the final expiration date or expiration date indicated

M. Confirmation results from the manufacturing division on whether the manufacturing control has been appropriately conducted

N. Release acceptance records from the quality division

O. Other matters required to be recorded regarding product manufacturing

(7) Confirmation, etc., of cells and tissues intended for use as raw materials: Paragraph 1, Item 4 prescribes that packaging and labeling materials are required for their appropriateness to be confirmed according to each lot (or according to each manufacturing number for those raw materials that do not compose a lot) or each control unit, and that those results are required to be recorded and stored. Raw materials are also required to be managed in a similar manner.

(8) The phrase "appropriately stored and released, and the records thereof shall be prepared" indicated in Paragraph 1, Item 5 regarding products, etc., and packaging and labeling materials shall mean the following:

A. Products, etc., and packaging and labeling materials shall be stored in clearly separated places.

B. Products, etc., and containers (those whose specifications and testing methods are specified in the marketing approval document or the official compendium) shall be stored with appropriate labeling (if stored under a condition of extremely low temperature, conformity of the labeling, etc., to this condition shall have been verified), categorization, etc., before and after testing. Disqualified products and containers as a result of testing shall be stored at a place clearly separated from other products and containers.

C. Labeling material shall be stored after inspection at the time of receipt. Measures of destructing, disposing, etc. shall be taken promptly for disqualified products as a result of testing.

D. Labeling material shall be categorized according to each item, stored via appropriate methods such as of preventing unauthorized access, and shall have their item name labeled at their respective storage area. Labeling material shall be issued only by predesignated personnel.

E. In cases of any change in description on the labeling material, measures shall be taken such as of prompt disposal of the labeling material prior to change.

F. Containers and packages labeled pursuant to the Act shall be managed in accordance to the above details in "C" through "E".

G. Products, etc., shall be stored in accordance to each of their storage conditions to avoid any influence on their quality, and shall also be stored in accordance to their storage conditions prescribed by their relevant laws and regulations.

H. Storage of raw materials and their receipt/distribution shall be recorded according to each lot (or according to each manufacturing number for those raw materials that do not compose a lot) and to each item.

I. Storage and receipt/distribution of products shall require records to be kept on the date of storage, number of products stored, measures taken during storage, date of release, number of products released, and shipping destination according to each lot (or according to each manufacturing number for those products that do not compose a lot) and each product.

J. Storage and receipt/distribution of packaging and labeling materials shall require records to be kept for each control unit and each item.

(9) Sanitary control of buildings and facilities: the following matters shall be given attention when ensuring "cleanliness" indicated in Paragraph 1, Item 6.

A. Necessary measures shall be taken to prevent contamination and cross-contamination due to products, etc., that have not been inactivated or eliminated, such as of inactivating and eliminating bacteria, fungi, and viruses each time an operation has been completed in a series of manufacturing process.

B. Drugs, etc., used for decontamination shall be those that have been validated with consideration of the resistance of the microorganism. However, cleaning conducted for decontamination of a different cell line of a same species or of a very similar virus, etc., may be validated using a representative cell line, etc., if there is no evidence indicating a remarkable difference in its resistance against the drug, etc., for decontamination.

(10) Inspection and maintenance of buildings and facilities, calibration of measuring equipment, etc.: Paragraph 1, Item 7 prescribes that buildings and facilities are required to be regularly inspected and maintenanced and to have these records kept and stored, and that calibration of measuring equipment are required to be appropriately conducted and to have these records kept and stored.

(11) Confirmation of appropriate manufacturing control and reporting of this result to the quality division: Paragraph 1, Item 8 prescribes that manufacturing control requires confirmation on their appropriate conduct via records on manufacturing, storage and receipt/distribution, and sanitary control, and that this result must be reported to the quality division in document.

(12) Setting and control of control level for operation environment, such as cleanliness level: Paragraph 1, Item 9 prescribes that work rooms or working control areas are required to have an appropriate control level set and controlled for their operation environment, such as cleanliness level, depending on the product type, structure, property, manufacturing process, and the content of the operation conducted at the work room or the working control area.

(13) Setting and control of control items for products, etc., and packaging and labeling materials: When conducting operations pertaining to those prescribed in Paragraph

1, Item 10 or to other process controls, attention shall be given to the matters specified in the marketing approval document and to such matters as the following:

A. Control levels and their acceptance criteria shall be set based on information obtained during the development stage and on the actual data.

B. The type and range of "control levels necessary for process control" shall be set with such consideration on the extent to which the product property, manufacturing process stage, and manufacturing process influence the product quality.

C. Matters regarding important process control shall be documented, including control methods, and their approval shall be obtained from the quality division.

D. Sampling shall be conducted via procedure that enables contamination and cross-contamination to be prevented between the obtained sample and the other product, etc., and that enables integrity of the samples to be assured after being obtained.

E. Testings pertaining to process control shall generally be subject to inspections pertaining to nonstandard testing results.

(14) Measures for preventing contamination of products, etc., due to microorganisms, etc.: "Necessary measures" indicated in Paragraph 1, Item 11 shall be such measures as the following:

A. From the perspective of preventing confusion, contamination, and cross-contamination, cells and tissues obtained from different donors or different donor animals shall not be handled at the same time in the same culture equipment.

B. In order to prevent contamination and cross contamination of products, etc., containment is required in manufacturing processes that may develop aerosol, such as in centrifuging or mixing.

(15) Setting and control of control levels necessary for process control: in relation to the provision of Paragraph 1, Item 12, environment monitoring program shall be one that is via a method that also enables recognition of contamination due to specific microorganisms according to the property of the product, etc.

(16) Control of water for manufacturing: Paragraph 1, Item 13 prescribes that water for manufacturing is required for its control level to be appropriately set and controlled

depending on its use, for those pertaining to necessary microbiological items and physicochemical items.

(17) Measures for preventing contamination due to products, etc., whose microorganisms, etc., have not been inactivated or eliminated: Paragraph 1, Item 14 prescribes that when inactivating or eliminating microorganisms, etc., contained in products, etc., during the manufacturing process, necessary measures are required to be taken to prevent contamination due to products, etc., whose microorganisms have not been inactivated or eliminated.

(18) Necessary measures for maintaining culture condition: Paragraph 1, Item 15 prescribes that when using biological technology in the manufacturing process, necessary items for controlling the manufacturing process, such as temperature and hydrogen ion index, are required to be continuously measured.

(19) Paragraph 1, Item 16 prescribes that when using a column chromatography device, etc., in the manufacturing process, necessary measures are required to be taken to prevent contamination of this device due to microorganisms, etc., and endotoxin is measured as necessary.

(20) Paragraph 1, Item 17 prescribes that when using a culture method that continuously supplies culture into the production reactor and continuously eliminates culture medium in the manufacturing process, necessary measures are required to be taken to maintain culture condition in the production reactor during cultivation.

(21) Disposal of articles, etc., contaminated with microorganisms, etc.: "Articles" prescribed in Paragraph 1, Item 18 shall possibly include documents and records that may have been contaminated due to microorganisms, etc., via droplets or exposure to aerosol.

(22) Control of cell lines for manufacturing, etc.: "Cell strains to be used for manufacturing" prescribed in Paragraph 1, Item 19 shall be, for example, cell lines intended for use as raw materials of human cell-processed products or of animal cell-processed products, packaging cell lines in which the plasmid vector or viral vector intended for use as raw materials of gene therapy products is transfected and cell lines used as feeder cells.

(23) Paragraph 1, Item 20 prescribes that biological raw materials of cellular and tissue-based products used in manufacturing the product are required to be

confirmed on whether they meet the conditions as raw materials according to the quality specifications in the approved product information described in the product master formula and the Standards for Biological Materials, and that those results are required to be recorded and stored.

(24) Creation and storage of records on biological raw materials of cellular and tissue-based products: The phrase "a firm collecting raw materials of the biological-origin raw materials for regenerative medicine products (referring to the origins of raw materials or materials (including those used during the manufacturing processes) to be used for manufacturing)" indicated in Paragraph 1, Item 21 shall mean vendors that collect or produce raw material and vendors that manufacture raw materials or intermediate products from raw materials (hereinafter referred to as "raw materials collecting firms, etc.").

(25) The phrase "shall be properly retained" indicated in Paragraph 1, Item 21 shall mean to take measures to prevent deletion, loss, and confusion of records, and to control records so that any necessary records may be taken out promptly.

(26) Paragraph 1, Item 22 prescribes that records are required to be taken on biological raw materials of cellular and tissue-based products and on reporting of manufacturing control results to the quality division according to each product lot (or according to each manufacturing number for those products that do not compose a lot), and that these records are required to be stored.

(27) Measures for preventing confusion and cross contamination of cells and tissues: The provision in Paragraph 1, Item 23 prescribes that in order to prevent confusion of cells or tissues and cross-contamination due to bacteria, fungi, viruses, etc., necessary measures are required to be taken, such as of avoiding cells and tissues obtained from different donors or different donor animals to be handled at the same time at the same place and of avoiding inappropriate storage that may have risk of confusion or cross-contamination. Regarding judgment on the "risk of cross-contamination", records on the results of confirmation at the time of obtaining the cells or tissues, prescribed in Paragraph 1, Item 24, shall be used when obtaining cells or tissues, and records on rearing control, etc., after obtaining donor animals, prescribed in Paragraph 1, Item 31, shall be used when obtaining, rearing, and sampling donor animals at manufacturing sites, and necessary measures shall be taken accordingly, such as of storing at an isolated place. "Necessary measures" prescribed in Paragraph 1, Item 23 shall be such measures as the following:

A. Cells or tissues, or donors or donor animals shall be differentiated and shall be controlled based on appropriate information for definitely preventing confusion (hereinafter referred to as "donor identification information"). Donor identification information shall be in symbols, numbers, etc., from which personal information, such as name and address of the donor, cannot be identified, and shall be one that may not cause any confusion.

B. Cells or tissues in the manufacturing process shall be handled during transfer, etc., in a state where donor identification information is labeled (culture containers, etc., shall be labeled directly) with at least the information necessary for definitely preventing confusion, and other necessary measures shall be taken, such as of providing training to relevant personnel.

C. When handling at the same time cells or tissues obtained from different donors or donor animals, those cells or tissues shall be ensured to be always appropriately corresponding to the donor identification information pertaining to them when being transferred, and necessary measures shall be taken with attention to the following matters in order to definitely prevent confusions.

(a) When initiating operations pertaining to cell or tissue culture, their donor identification information (including information pertaining to identification of source region, etc., as necessary) shall be clearly labeled according to each culture device (or according to each container if multiple containers are used within a single culture device). This label shall be discarded at an appropriate timing so as not to cause any confusion.

D. When using culture device, necessary information shall be recorded and stored in order to definitely prevent confusion.

E. When releasing the final product, necessary information shall have been obtained and recorded, such as on the names of the institution, medical department, and physician of the medical institution, etc., at which the patient will receive transplantation, etc. (hereinafter referred to as "information on shipping destination"), in order for the product to be definitely provided to this patient.

(28) Paragraph 1, Item 24 prescribes that when obtaining human or animal cells or tissues (excluding those that have records of use and are derived from cell cultures initiated from characterized cell banks) as raw materials, those raw materials are

required to be confirmed regarding whether they are in accordance to the product master formula of the product, using the recorded matters indicated in the records, etc., prescribed in the Standards for Biological Materials, and those confirmation results shall be recorded and stored.

(29) "Facilities where the cells or tissues have been collected" indicated in Paragraph 1, Item 24 (a) shall mean the medical institution, etc., at which the cells or tissues were obtained from a donor, or the institution at which cells or tissues were obtained from a donor animal.

When confirming via records regarding this matter, attention shall be given to the fact that the "1 Standards for Human Cell and Tissue Materials" (1) of "Chapter 3 General Rules for Human-derived Materials" and in the "2 Standards for Animal Cell and Tissue Materials" (1) of "Chapter 4 General Rules for Animal-derived Materials" in the Standards for Biological Materials prescribes that human cellular and tissue raw materials, etc., and animal cellular and tissue raw materials, etc., "are required to be those that have been obtained from an institution with sufficient personnel and facility to conduct sanitary control necessary for obtaining those raw materials".

(30) When confirming via records regarding the matter prescribed in Paragraph 1, Item 24 (c), attention shall be given to the "1 Standards for Human Cell and Tissue Materials" (3) of "Chapter 3 General Rules for Human-derived Materials" in the Standards for Biological Materials, and to the provisions pertaining to donor qualification in its operational notification, etc.

(31) When confirming via records regarding the matter prescribed in Paragraph 1, Item 24 (d), attention shall be given to the "2 Standards for Animal Cell and Tissue Materials" (3) of "Chapter 4 General Rules for Animal-derived Materials" in the Standards for Biological Materials, and to the provisions pertaining to donor animal qualification in its operational notification, etc.

(32) When confirming via records regarding the matter prescribed in Paragraph 1, Item 24 (e), attention shall be given to the "1 Standards for Human Cell and Tissue Materials" (2) of "Chapter 3 General Rules for Human-derived Materials" and to the "2 Standards for Animal Cell and Tissue Materials" (2) of "Chapter 4 General Rules for Animal-derived Materials" in the Standards for Biological Materials, as well as to the provisions pertaining to measures for when obtaining human cellular

and tissue raw materials, etc., or animal cellular and tissue raw materials, etc., in their operational notifications, etc.

(33) Records regarding "the course of shipping the cells or tissues" prescribed in Paragraph 1, Item 24 (f) shall be those that enable confirmation of whether shipping conditions, such as shipping containers and shipping procedures (including temperature control, shipping time control, etc.), are being complied with during the course of shipping until receipt of the cells or tissues.

(34) Records regarding "matters necessary for ensuring product quality" prescribed in Paragraph 1, Item 24 (g) shall be, for example, the following records:

A. Records on the identification number of the donor

B. Records on necessary matters (including the following matters) from the "1 Standards for Ruminant Animal-derived Materials" (2) of "Chapter 4 General Rules for Animal-derived Materials" in the Standards for Biological Materials

(a) Country of origin

(b) Production date of raw material

(c) Rearing and slaughtering state of ruminants intended to be used as the source of raw material

(d) Course of processing and operating raw material for prevention of transmissible spongiform encephalopathies

(e) Lot number of raw material

C. Lot number of animal cellular and tissue raw materials, etc., and other necessary records on matters from the "2 Standards for Animal Cell and Tissue Materials" (5) of "Chapter 4 General Rules for Animal-derived Materials" in the Standards for Biological Materials.

D. Records on testing results of reagents intended to be used in the manufacturing.

(35) Measures for preventing contamination of cells and tissues intended for use as raw materials due to microorganisms, etc.: the phrase "measures necessary for preventing contamination due to microorganisms, etc., during the course of collecting" prescribed in Paragraph 1, Item 25 shall mean measures that are required to be taken when collecting ruminant-derived raw materials, etc., and

animal cellular and tissue raw materials, etc., prescribed in "Chapter 4 General Rules for Animal-derived Materials" in the Standards for Biological Materials.

(36) Knowledge, etc., of shipping destination (institution name), date of distribution, and lot number or manufacturing number according to each product: Paragraph 1, Item 26 prescribes that knowledge of the shipping destination (institution name) and date of distribution are required to have been obtained according to each product and each lot (or according to each manufacturing number for those products that do not compose a lot; the same shall apply hereinafter in this Paragraph), in order to obtain information necessary for ensuring safety when any adverse event occurs in patients, etc., and when any problem occurs in the product, and prescribes that these records are required to be stored according to each lot of the manufactured product. Raw materials shall also be controlled in the same manner.

(37) Necessary measures, etc., for ensuring product quality in shipping: The phrase "necessary measures for ensuring product quality in shipping", indicated in Paragraph 1, Item 27 shall be, for example, to confirm whether shipping conditions, such as shipping containers and shipping procedures (including temperature control, shipping time control, etc.), are being complied with during the course of shipping and to confirm whether the storage conditions specified in the marketing approval document are being maintained.

(38) Paragraph 1, Item 28 prescribes that records are required to be kept and stored according to each lot (or according to each manufacturing number for those products that do not compose a lot) regarding the confirmation results at receipt of cells and tissues intended for use as raw materials, their measures for preventing contamination during the process of collecting, shipping destination (institution name), etc., of the product, and quality assurance measures for products, etc., during shipping.

(39) Paragraph 1, Item 29 prescribes that entry prohibition of persons into the work area (including those other than the personnel), control of clothes changing, control of health care, and other sanitary control necessary for preventing contamination and cross-contamination of products are required.

(40) "Strict procedures", indicated in Paragraph 1, Item 29 (c), shall include, for example, appropriate measures for preventing infections, such as of having employees who may be infected by pathogens to receive appropriate vaccines, and if necessary, to

be regularly examined and to receive additional vaccines. In order to definitely prevent confusions especially when handling at the same time cells or tissues that were obtained from different donors or different donor animals, culture device or its work room, etc., shall be handled by limited employees by means of keys, personal identification number, etc.

(41) When manufacturing products using human cells or tissues as raw materials, employees shall be vaccinated with hepatitis B vaccine, etc., as necessary.

(42) Employees engaged in the operation indicated in Paragraph 1, Item 29 (c) shall be forbidden to enter work rooms and working control areas in which operations with high risk of contamination or cross-contamination are conducted (including operations for establishing seed-lots or cell banks).

(43) Engagement restriction and other operation control of employees: Paragraph 1, Item 29 (d) prescribes that contamination or cross-contamination of manufacturing process are required to be prevented regarding those that occur via employees engaged in operations pertaining to control of animals used other than in the manufacturing process (including process pertaining to testing).

(44) Sanitary control of personnel: Paragraph 1, Item 30 prescribes that sanitary control is required for personnel who conduct operations in controlled clean areas or aseptic operation areas.

(45) Regarding engagement restriction of personnel prescribed in Paragraph 1, Item 30 (e), personnel who were engaged in operations that expose them to cells, tissues, microorganisms, etc., during a day are generally required to not transfer from that work room to other work rooms that handle different cells or tissues, work rooms that handle products that have completed the process of inactivation, work rooms pertaining to manufacturing of other products, or working control areas. If such transfer is inevitable, quality risk management shall be used to take measures for preventing contamination and cross-contamination.

(46) Other necessary operations for manufacturing control: "Other duties necessary for manufacturing control" indicated in Paragraph 1, Item 31, shall mean, for example, the following operations:

A. Necessary measures shall be taken to prevent confusion in manufacturing control. For example, these "measures" before initiating manufacturing

operations shall include, for example, measures to assure that no products, etc., packaging and labeling materials, documents, records, etc., exist regarding those that are unnecessary in initiating operations pertaining to manufacturing control.

B. Records on rearing control, etc., after obtaining donor animals shall be taken and stored. Of the information necessary for judging whether the animal cellular and tissue raw materials, etc., are sufficiently qualified for their provision, and information necessary for ensuring quality and safety of ruminant-derived raw materials and animal cellular and tissue raw materials, etc., which are prescribed in "Chapter 4 General Rules for Animal-derived Materials" in the Standards for Biological Materials, "records on rearing control, etc., after obtaining donor animals" stated here shall be such records on information pertaining to rearing control and slaughtering, and on identification control of donor animals, observation for their abnormalities, isolation of abnormal animals, and judgment of whether to continue using animals that came in contact with abnormal animals. Provisions in Paragraph 1, Item 25 shall be referred to regarding measures necessary for preventing contamination due to microorganisms, etc., during the process of collecting cells or tissues intended for use as raw materials from donor animals.

C. In case of any accident, necessary measures shall be taken for product manufacturing control. For example, appropriate measures shall be established in advance with the assumption of various risks, such as manufacturing loss of products pertaining to human (auto) cell processed products, and with consideration of using risk management.

D. Results reported from the quality division on product, etc., and material testings shall be notified to relevant sections of the manufacturing division.

(47) Paragraph 2 prescribes that when manufacturing a product, records shall be controlled to enable tracking of all stages, from the time of collecting raw material to handling of things that come in contact with the product, etc., and shipping from manufacturing sites, in order for the relevant product to be immediately identified and for their cause to be investigated in case any problem in the product, etc., or material was found or in case infection occurs due to the product.

12. Article 12 (Quality Control)

(1) This Article prescribes matters regarding operations pertaining to quality control that manufacturers have the quality division conduct. When conducting these operations, use of quality risk management shall be put into consideration as necessary.

(2) Storage of reserve samples: Storage of reserve samples prescribed in Paragraph 1 shall be in accordance to the following:

A. "Reserve sample" stated here shall be products (limited to those used for determining release into the market as prescribed in Article 9, Paragraph 2 as applied mutatis mutandis to Article 21 of GQP Ordinance (hereinafter referred to as the "final product")) that are stored under an appropriate storage condition at an amount that enables prescribed testings (excluding test for extractable volume) to be conducted twice or more (or an amount that enables appropriate testings for sterility testing, endotoxin testing, and mycoplasma testing) in case any malfunction of the cellular and tissue based product was found after release into the market. "An amount twice or more than the necessary amount for prescribed testing" pertaining to storage of reserve sample of a product, etc., in which one year has elapsed after its shelf life shall be an amount twice or more than as that necessary for testing pertaining to investigation for the cause of, for example, viral infection.

B. In order for infection-related viruses, abnormal prion, unidentified substances, etc., to be detected with higher sensitivity, there may be cases where it is necessary to consider having intermediate products, etc., become subject to storage of reserve sample at an appropriate stage.

C. For products pertaining to specified regenerative medicine products that do not compose a lot, biological raw materials of cellular and tissue-based products shall be stored as the reserve sample by the manufacturer or by the raw materials collecting firms, etc. at an amount twice or more than the necessary amount for testings pertaining to investigation for, for example, the cause of viral infections (or an appropriate amount if there is difficulty securing the amount), and shall be stored according to each manufacturing number of the product if the biological raw materials of cellular and tissue-based products and the product corresponds one-on-one, or according to each lot of biological raw materials of cellular and tissue-based products if the biological raw

material of cellular and tissue-based products of a single lot is used in multiple products. When having raw materials collecting firms, etc. conduct the storage, this shall be appropriately conducted upon agreements regarding storage amount, storage condition, etc.

(3) "Required inspection and testing" indicated in Paragraph 1 shall mean the testings indicated in the product master formula. "Appropriate storage condition" shall mean, in principle, an appropriate condition with consideration of the storage condition during general marketing in the form shipped into the cellular and tissue-based product market pertaining to the relevant product (or in the form of a packaging with similar function as those shipped into the market if there is any inevitable reason, such as due to high capacity).

(4) "Raw materials collecting firms, etc." indicated in Paragraph 1 shall be, for example, vendors that collect or produce raw materials, and vendors that manufacture raw materials or intermediate products from raw materials.

(5) Storage period of the reserve sample of products pertaining to specified regenerative medicine products prescribed in Paragraph 1, Item 1, shall be 10 years plus their shelf life to enable their use in investigating the cause of infections, including those that are unidentified, for the purpose of safety measures.

(6) "Appropriate duration" indicated in Paragraph 1, Item 2 shall be an appropriate period set for each product under the responsibility of the manufacturers in order to prepare for any future confirmation required to be conducted on product quality, such as when malfunction was found in the cellular and tissue-based product after being released into the market.

(7) Sampling, etc., at testing of products, etc., and packaging and labeling materials: Sampling prescribed in Paragraph 2, Item 1 shall, in principle, be conducted by personnel from the quality division. However, if sampling is required to be conducted aseptically or to be conducted depending on the current state of process, or if there is any other rational reason, the actual sampling may be conducted by personnel from the manufacturing division who have gone through necessary training and have been designated by the quality division under its responsibility via an appropriate method that it has approved. Sampling shall be conducted with attention to the following matters:

A. The collected sample shall be a representative of its lot or its control unit.

B. The number of containers subject to sampling, the sampling area within the subject container, and the sampling amount from each container shall be determined with consideration of the risk on product quality and of the product property.

C. The number of containers subject to sampling and the number of samples (sample size) shall be determined based on the importance and homogeneity of the product, etc., and material intended for sampling, history pertaining to the quality of the raw material and material that the supplier provided in the past, and the necessary amount for appropriate testing.

D. Sampling shall be conducted at a predesignated place via procedures that will prevent contamination of the sampled product, etc., and material, and cross-contamination between the product, etc., material, and other things.

E. Containers that were subject to sampling shall be handled with care when opening and shall be immediately closed after sampling.

F. Containers of the product, etc., and material after sampling shall be labeled with an indication that sampling has been conducted.

(8) If highly invasive in donors and the possible amount of sampling is small, or if there is any other difficulty in the necessary sampling, testing may be conducted after growing the samples or be substituted by confirmation in testing pertaining to quality control of the product of its lot number or manufacturing number pertaining to the relevant sample (may be substituted by testing pertaining to a validated process management).

(9) Records of sampling (sampling records) prescribed in Paragraph 2, Item 1 shall indicate the following matters. However, if these matters are indicated in the testing records, a separate sampling record will not be required.

A. Sample name

B. Lot number or manufacturing number, or control number

C. Date of sampling and the name of person who conducted the sampling

(10) Records of testing (testing records) prescribed in Paragraph 2, Item 2 shall require the following matters to be indicated:

A. Sample name

B. Lot number or manufacturing number, or control number

C. Testing items, date of testing, name of person who conducted the testing, and the testing results

D. Assessment details of testing results, date of assessment, and the name of the person who conducted the assessment

The above testing records shall be created at the manufacturing site that conducts the manufacturing operations of the product pertaining to the relevant testing, even in cases of testing conducted, for example, by an external testing institution. In this case, the "name of the person who conducted the testing" may be substituted by the "name of external testing institution, etc.", and the "request date for testing" and the "receipt date of testing results" shall be indicated together with the "date of testing" and the "date of assessment".

(11) To conduct the "inspection and testing implemented on the responsibilities of the manufacturers, etc. using other inspection and testing facilities of the manufacturers, etc. or other inspection and testing institutions" indicated in Paragraph 2, Item 2 shall mean to have personnel of the manufacturers to conduct the testing using an external testing institution, etc., or for the manufacturers to request an external testing institution to conduct the testing and to assess those results under its own responsibility. When conducting testings via these methods, agreement with the external testing institution, etc., shall be concluded in advance on necessary matters, such as communication method, necessary technical conditions for entrusting the testing, and quality control methods during shipping of the samples, and the following measures shall also be taken:

A. List of items/products to be requested for testing (Form No. 3-3-1 or Form No. 3-3-2) shall be created and stored at the quality division according to each product, etc., or material. Matters in the list shall be modified accordingly whenever there is any change.

B. When requesting testing, a request form for testing (Form No. 3-3-3) shall be submitted together with information on sample specification and testing method, and a necessary amount of sample shall be sent. When sending samples, following matters shall be labeled on them:

(a) Sample name

(b) Lot number or manufacturing number, or control number

(c) Name of manufacturing site

(d) Cautions for storage

(e) Other necessary matters

(12) If there is difficulty sterilizing the product, etc., the culture media, additives (serum, growth factors, antibiotics, etc.), and other raw materials shall be confirmed that there is no contamination with microorganisms, etc., or other cells or tissues, and other necessary measures shall be taken to prevent contamination and cross-contamination of the product, etc.

(13) Inspection and maintenance of facilities and equipment for testing, calibration of measuring equipment, etc.: Paragraph 2, Item 3 prescribes such matters as those regarding regular inspection and maintenance of facilities and equipment for testing, and calibration of measuring equipment for testing.

(14) Assessment of testing results, etc.: Paragraph 2, Item 4 prescribes matters regarding assessment of testing results and document reporting of those results to the manufacturing division.

If testing of a raw material requires many days, manufacturing may be conducted using this raw material without waiting for the quality division to send a document reporting of the testing results to the manufacturing division as long as the following requirements are met:

A. Quality risk management is used and quality risk (including quality risk that influences other lots) is appropriately evaluated and controlled for those that are associated with the use of raw materials that may be disqualified.

B. Release acceptance by the quality division pursuant to the provisions in Article 13 shall be made via assessing the testing results as conforming, and this shall be prescribed in the operating procedure, etc.

(15) Identification and categorization methods of samples: Paragraph 2, Item 5 prescribes that samples are required to be categorized by appropriate identification labeling in order to prevent confusion and cross-contamination of the samples.

(16) Testing conducted at an appropriate stage of manufacturing for those that cannot be conducted on the product: Paragraph 2, Item 6 prescribes that testings are required

to be conducted at an appropriate stage of the manufacturing process for those that are important in terms of quality control and cannot be conducted on the product.

(17) Disposal of articles, etc., that have been contaminated with microorganisms, etc.: Paragraph 2, Item 7 prescribes that all articles, etc., contaminated with microorganisms, etc., during the process of testing are required to be disposed of in order to prevent risk of sanitary problem.

(18) Control of cell lines, etc., for testing: Paragraph 2, Item 8 prescribes matters regarding creation and storage of records on cell lines, etc., used in testing.

(19) Creation and storage of records on testing results: Paragraph 2, Item 9 prescribes that testing results are required to be recorded and stored according to each product lot (or according to each manufacturing number for those products that do not compose a lot).

(20) Testing, etc., at receipt and after receipt of donor animals: Paragraph 2, Item 10 and Item 11 prescribe matters regarding testing at receipt and after receipt of donor animals, and records, etc., of this operation. The phrase "testing at receipt and after receipt of donor animals" indicated in Paragraph 2, Item 10 shall be one that provides necessary information for ensuring quality and safety of animal cellular and tissue raw materials, etc., prescribed in "Chapter 4 General Rules for Animal-derived Materials" in the Standards for Biological Materials.

(21) Other necessary operations for quality control: "Other duties necessary for quality control" indicated in Paragraph 2, Item 12 shall be, for example, the following operations:

A. Other than operational measures prescribed in Paragraph 2, Item 5, necessary measures shall be taken to prevent confusion in quality control. These "measures" shall include, for example, measures to assure that no products, etc., packaging and labeling materials, documents, records, etc., exist regarding those that are unnecessary in initiating operations pertaining to manufacturing control.

B. Control of suppliers of raw materials and packaging and labeling materials

The following controls are required for suppliers of raw materials and packaging and labeling materials. Although "suppliers" generally refer to manufacturers, agents, brokers, traders, distributors, etc., of raw materials and

packaging and labeling materials, and also include, for example, medical institutions, etc., at which cells or tissues are collected from donors, here, agreements are required with those suppliers from which appropriate information can be obtained, and are not necessarily required with all suppliers. If there is difficulty receiving information on a specific lot from manufacturers of raw materials or packaging and labeling materials, measures shall be taken to enable receipt of appropriate information, such as concluding agreements with agents, etc., with consideration of the actual state of distribution.

(a) Raw materials and packaging and labeling materials shall be purchased from suppliers approved by the quality division and shall be obtained after confirming that they conform to pre-established standards. These details shall be indicated such as in the product master formula.

(b) Matters regarding important raw materials and packaging and labeling materials shall have agreements be concluded with the supplier regarding their manufacturing and quality.

(c) Manufacturing and quality controls shall be appropriately confirmed depending on quality risk on whether they are conducted in accordance to the details that were agreed with the supplier.

The phrase "shall be confirmed depending on quality risk" stated here shall mean the initial confirmation as well as continuous confirmations that are conducted depending on how much those raw materials and packaging and labeling materials influence product quality, depending on product quality review results of the raw materials and packaging and labeling materials, and on the state of change control and deviation control.

C. Storage of reserve sample pertaining to raw materials and packaging and labeling materials

Storage of "reserve sample" of the final product is a requirement prescribed in Paragraph 1, and of the packaging and labeling materials that may possibly influence the raw material and the quality of the product that has been released into the market, those packaging and labeling materials that require quality assurance are required for their reserve sample to be stored. Raw materials and packaging and labeling materials that should be stored as reserve sample shall be determined by the manufacturers with consideration of quality risk and