Provisional Translation (as of April 2025)*

PMSB Notification No. 1314

December 26, 2000

To: All Prefectural Governors

Director of Pharmaceutical and Medical Safety Bureau,

Ministry of Health and Welfare

Ensuring the Quality and Safety of Drugs, etc. Manufactured from Raw Materials of Human or Animal Origin

Regarding pharmaceuticals, medical devices, regenerative medical products, quasi-drugs and cosmetics (hereinafter referred to as "drugs, etc.") manufactured from raw materials of human or animal origin, manufacturers, importers, distributors, and in country representatives of foreign manufacturers (hereinafter referred to as "manufacturers, etc.") shall take measures to ensure quality and safety based on the current scientific standards. The "Basic Concepts on the Handling and Use of Drugs Containing Cells or Tissue" (hereinafter referred to as the "Basic Concepts") and the "Guidelines for Ensuring the Quality and Safety of Human-derived Cell/Tissue-processed Products" (hereinafter referred to as the "Guidelines") was adopted by the Subcommittee in Attachment 2[1]. Both documents were compiled by the Special Subcommittee on Biotechnology of the Central Pharmaceutical Council.

It has been decided to conduct voluntary inspections by Manufacturers, etc. and maintenance of approval documents. Please direct the relevant organizations under your jurisdiction accordingly.

[1] Appendix 2 is delated since 'the Guideline' is revised as 1) Guidelines on ensuring quality and safety of products derived from processed cell and tissue (Autologous cells), PFSB Notification No. 0208003, 2008 and 2) Guidelines on ensuring quality and safety of products derived from processed cell and tissue (Allogeneic cells), PFSB Notification No. 0912006, 2008 on February 8, 2008.

*This English translation of the Japanese Notification is intended to be a reference material to provide convenience for users. In the event of inconsistency between the Japanese original and this English translation, the former shall prevail.

1. Scope

The scope of human or animal-derived drugs, etc. is as follows, excluding blood preparations listed in the Minimum Requirements for Biological Products and those not exclusively used directly in the human body (e.g., *in vitro* diagnostic products).

(1) Drugs, etc., composed of human or animal cells or tissues

(2) Drugs, etc., containing ingredients derived from extracts or secretions from human or animal cells or tissues

(3) Drugs, etc., containing ingredients derived from extracts from human or animal urine.

(4) Drugs, etc., manufactured by applying cell culture or genetic modification technology to human or animal-derived cells

(5) Drugs, etc., manufactured using ingredients (1) through (4) as additives (including culture media in the manufacturing process)

2. Handling and Use of Human or Animal-derived Drugs, etc.

For pharmaceuticals, medical devices and regenerative medical products falling under (1) of 1, the Ministerial Ordinance will be revised or new standards will be established based on the "Basic Concepts" in the future, but for drugs, etc. falling under any of (2) through (5), raw material handling and manufacturing control should be conducted according to Chapters 2 (2-1, 2-4 through 2-6), 3 and 4 of the "Basic Concepts" in the Attachment 1.

3. Voluntary Inspection

(1) Manufacturers are responsible for ensuring the quality and safety of drugs, etc. and should review manufacturing processes, specifications, etc. in accordance with advances in science and technology.

(2) In conducting voluntary inspections, from the viewpoint of ensuring quality and safety, manufacturers, etc. are responsible for ensuring that the details of donor screening (including test items and methods) carried out on humans or animals providing raw materials, inactivation/removal treatment of bacteria, fungi, viruses, etc. during the manufacturing process are properly carried out from the perspective of preventing the spread of infectious diseases in light of the current level of science and technology.

(3) When conducting voluntary inspection, manufacturers should confirm that appropriate manufacturing and quality control is being conducted, including raw materials, taking into consideration the route of administration and the site of application of the product.

4. Handling of Approval Documents

(1) The quality and safety of drugs, etc. manufactured from raw materials of human or animal origin shall be ensured through appropriate manufacturing and quality control, including raw materials. The following items must be clearly stated in the approval document, and therefore, a partial change approval should be filed as maintenance of the approval document as necessary.

a. Origin of human or animal-derived ingredients used as raw materials.

b. Details of donor screening (including test items and methods)

c. Methods of inactivation/removal treatment of bacteria, fungi, viruses, etc. during the manufacturing process.

d. Manufacturing processes considered important from the viewpoint of ensuring quality and safety.

(2) If, as a result of the voluntary inspection, additions or changes are to be made to donor screening or inactivation/removal treatment of bacteria, fungi, viruses, etc., an application for partial change approval of the approved items should be submitted.

In addition, if the necessary donor screening or inactivation/removal treatment of bacteria, fungi, or viruses, etc., cannot be added or changed, the necessary procedures such as submission of an approval cancellation notification should be performed.

(3) Since the policy is to promptly review applications for partial change approvals for the maintenance of these approval document and voluntary inspections, voluntary inspections should be conducted by the end of March 2001, and the results of the implementation should be summarized. In addition, applications for partial change approval, which are required, shall be filed by the end of March 2002.

(Attachment 1)

Basic Concepts on the Handling and Use of Drugs Containing Cells or Tissue

Chapter 1: General Provisions

1.1. Objective

With regard to drugs containing cells or tissue, there is concern about the risk of transmission of infectious diseases caused by cells or tissues. Therefore, it is essential to use raw materials that are not contaminated by bacteria, fungi, viruses, etc., and to prevent contamination during the manufacturing process. It is also necessary to prevent the production of defective products due to improper manufacturing and the occurrence of problems due to improper handling or use of products. Therefore, from this perspective, it is necessary to implement consistent measures from the collection of cells or tissues to their manufacture and use.

The purpose of this document is to provide the basic requirements for handling cells and tissues, and to ensure the quality and safety of drugs containing cells or tissue and the scientific and ethical validity of the handling of cells and tissues.

If a method other than those indicated in this document is to be used, the necessity and appropriateness of the method from the viewpoint of ensuring quality and safety must be explained and the rationale for the method must be provided.

The items described in this document apply not only after the approval of a drugs containing cells or tissue, but also during clinical trials.

1.2. Basic Principle

Drugs containing cells or tissue should be used when their usefulness is comparable or superior to that of other drugs or therapies, because the risk of transmission of infectious diseases caused by cells or tissues may not be completely eliminated.

1.3. Definitions

The definitions of terms in this Basic Concept are as follows

1. The "drugs containing cells or tissue" indicates a biological drug, biological medical device or regenerative medical product that is composed of human or animal cells or tissues, and includes drugs, medical devices and regenerative medical products made from one's own cells or tissues but does not include blood preparations.
2. The "donor" is a person who donates cells or tissues that are used as raw materials, etc. of drugs,

etc. [excluding the body of a brain-dead person stipulated in Article 6, Paragraph 2, the Organ Transplantation Law (Law No. 104, 1997)].

3. The “donor animal” is an animal other than human that provides cells or tissues that are used as raw materials, etc. of drugs, etc.
4. The "legal representative" indicates a person who gives consent on behalf of the donor in cases where the donor is unable to give full consent or lacks the capacity to give full consent independently, and indicates a person with parental authority, a spouse, a guardian, or other person who is equivalent thereto over the donor, if the donor is still alive.
5. The “donor screening” is to determine whether donor or donor animal is sufficiently eligible to donate cells or tissues that are used as raw materials, etc. of drugs, etc. by diagnoses based on interview, tests, etc. for donor and by tests and breeding control for donor animal.
6. The “window period” is a period in the initial stage of infection during which it is impossible to detect any pathogens including bacteria, fungi, viruses, etc. or their antigens, antibodies, genes, etc.
7. The "work zone" indicates an area where drugs containing cells or tissue are directly handled and manufacturing operations are conducted.

Chapter 2: Cell and Tissue Collection

2.1. Collection Medical Institution

Cells and tissues must be collected at a medical institution that meets the following requirements or that meets the equivalent or higher to the following ones.

1. The institution must have the hygienic management necessary for the collection and preservation of cells and tissues, and personnel with sufficient knowledge and skills in collection.
2. In the case of collection of human cells or tissues, an ethics committee must be established to investigate and deliberate on the appropriateness of the collection.
3. The following requirements must be met for the ethics committee specified in 2.
   (1) A system to sufficiently deliberate on the collection of cells and tissues from ethical and scientific viewpoints must be secured.
   (2) Rules regarding the method of operation must be established and made publicly available.
   (3) Committee members must include experts in ethics and/or law, experts in science, and citizens.
   (4) With regard to the participation of outsiders, experts in ethics and law, or citizens, it is necessary to keep the composition of the committee members at an appropriate ratio, taking into consideration the number of members of the committee as a whole.
   (5) The head of the facility, the person who collects cells or tissues, and persons with a close relationship to the person requesting the collection of cells or tissues must not participate in the

deliberations and voting.

(6) The ethics committee must not hold a meeting for deliberation or voting unless at least one expert in ethics and/or law or in a civil is present.

4. Manufacturers, importers, distributors and in-country representative of foreign manufacturers (hereinafter referred to as "manufacturers, etc.") who use the collected human cells or tissues are also required to establish a committee in accordance with 2, and should be receive investigation and deliberation on cell and tissue usage from ethical and scientific perspectives.

2.2. Explanation, Consent for Cell and Tissue Collection

1. Written Explanation and Obtaining Consent

Before conducting donor screening, the person who collects cells or tissues must provide the prospective donor with sufficient explanation in writing so that the prospective donor understands the purpose of cell or tissue usage, protection of personal information, and other matters related to collection, and must obtain consent in writing of his/her own free will.

When explaining, it shall be made clear that the person has the right to refuse or withdraw consent, and that the person will not be treated unfavorably even if he/she refuses or withdraws consent.

2. Legal representatives

In cases where the donor is unable to give informed consent or lacks the ability to give full consent on his/her own, cells or tissue collection may be conducted with the consent from a legal representative only when the following requirements are met.

(1) There are reasonable grounds that the collection of cells or tissues from the donor is necessary from the perspective of ensuring the quality and safety of the drugs containing cells or tissue.

(2) The legal representatives must be a person who is judged to best represent the donor's will and interests, and when obtaining consent from a legal representative, a record of the relationship between the donor and the legal representatives must be made and kept with the consent form.

(3) In this case, the person who collects the cells or tissues should, as far as possible, provide the donor with explanations appropriate to his or her capacity to understand, and should also make efforts to obtain consent from the donor himself or herself.

(4) The scientific and ethical appropriateness of the collection of cells or tissues from the donor has been reviewed and approved by the ethics committee of the medical institution where the collection is to take place.

3. When the donor is deceased

When cells or tissues are to be donated from a deceased person, the bereaved family should be informed and consent should be obtained in accordance with 1. The collection of cells or tissues should be limited to cases in which the donor has not refused the donation of cells and tissues while the donor was alive.

4. When using the cells or tissue enucleated during surgery

In cases where cells or tissues enucleated during surgery, consent should be obtained in accordance with 1 and 2. In such cases, collection of cells or tissue must not be given priority for the purpose of the surgery.

5. Animal Welfare

Persons who collect cells or tissues from donor animals must obtain approval from the animal welfare committee at the facility where the collection is to be conducted and conduct it in the spirit of animal welfare.

2.3. Donation without Compensation

Donation of cells or tissues from donors shall be made without compensation. However, this does not apply to the donor's cost arising from the donation of cells and tissues, provided that appropriate compensation is made with the approval of the ethics committee, taking into consideration the actual costs incurred, such as transportation expenses.

2.4. Selection Criteria and Eligibility of Donors and Donor Animals

1. Donors (Human)

(1) When collecting cells or tissues, a medical interview and other diagnostic and testing procedures should be conducted depending on the purpose of use in order to confirm eligibility for cells or tissue donation.

In particular, infection with hepatitis B virus (HBV), hepatitis C (HCV), human immunodeficiency virus (HIV), human T-cell leukemia, and parvovirus B19 must be ruled out by medical interview and tests (serological tests and nucleic acid amplification tests, etc.). Infection with Cytomegalovirus and EB virus should be denied by tests, if necessary.

In addition, the eligibility of the donor for the following conditions should be determined based on the patient's medical history, medical interview, and whether or not the patient has received blood transfusions or transplantation.

- Bacterial infections, such as syphilis (Treponema pallidum), chlamydia, gonorrhea, and tubercle bacillus
- Sepsis or suspected sepsis
- A malignant neoplasm
- Serious metabolic and endocrine disorders
- Collagen and blood diseases
- Hepatic diseases

・ Dementia (confirmed or suspected transmissible spongiform encephalopathy (TSE))

However, donor screening is not necessarily required when autologous cells or tissues are used.

(2) The most appropriate test method at the time should be used.

The test items and methods should be reviewed as needed in light of new findings on infectious diseases and advances in science and technology.

(3) When conducting donor screening, retests should be conducted at the most appropriate time possible, taking window periods into consideration, depending on test items and/or test methods.

2. Donor (animals)

(1) Microbiological characteristics of each animal species, such as endogenous retroviruses, should be considered when selecting animal species.

(2) In order to avoid transmission of zoonotic disease, the appropriateness of cells or tissues to be collected should be ensured through appropriate tests at the animal receiving and husbandry management after receiving the animals.

(3) In the housing and management of donor animals, standard operating procedures should be prepared in advance for each operation.

In addition, donor animals should be kept in a facility with appropriate equipment, such as containment equipment to prevent the transmission of infectious diseases to the donor animals.

(4) Criteria for determining the items and eligibility of tests to be conducted at the animal receiving and during housing management, should be established in advance.

In particular, regarding tests for infectious diseases, etc., it is important to note that the items to be tested vary depending on the animal species.

(5) Personnel handling donor animals should handle them in the spirit of animal welfare.

2.5. Ensuring the Appropriateness of Collection Operations

1. When collecting cells or tissues, necessary measures should be taken to prevent contamination by microorganisms, etc. during the collection process.

   If necessary, appropriate tests for bacterial, fungal, viral, or other contamination of the collected cells or tissues shall be performed to deny microbial contamination or the presence of bacteria, fungi, viruses, or other contaminants at the time of collection. Test items and testing methods should be reviewed as needed in light of new findings on infectious diseases and advances in academics and technology.

2. When collecting cells and tissues from a deceased donor, care should be taken to maintain courtesy to the donor.

2.6. Records

1. Records shall be made in the implementation of donor screening, acceptance examination of donor animals, housing management, in the implementation of collection operations, and in the examination of collected cells or tissues.
2. Cells or tissues to be used as raw materials must have the following records that can be verified. The records to be verified include the name of the collection medical institution or collection facility, minutes of ethics committee meetings, informed consent documents, written consent forms, date of collection, diagnosis and test results for donor screening, acceptance records for animals, housing management records, records of collection operations.

   In addition, if necessary, a system should be secured to obtain information on the onset of late-onset infection of the donor even after the donation of cells or tissues.
3. In general, the records listed in 2. should be stored at least 10 years after the product expiration date.

   In addition, for the purpose of confirming the success or failure of product manufacturing or treatment, or in order to investigate the cause of infection in patients, if it occurs, appropriate samples such as a part of cells or tissues collected should be stored for an appropriate period.

Chapter 3: Measures to Ensure Safety at the Manufacturing Stage

3.1. Quality Control System

1. Facilities that handle raw materials of drugs containing cells or tissue, cells or tissues in the manufacturing process, and final products shall establish a consistent quality control system depending on the characteristics of the products.
2. Facilities and equipment necessary for receiving raw materials, processing, and storing intermediate and final products in the manufacturing of drugs containing cells or tissue shall be provided, and these work zones shall be separated from other work zones.
3. To avoid the risk of mistakes and transmission of bacteria, fungi, viruses, cells and tissues from multiple donors must not be handled in the same room at the same time during the manufacturing process, nor must storage methods be used that cause cross-contamination.

3.2. Standard Operating Procedures

Standard operating procedures must be prepared for each operation performed in the manufacturing process.

When preparing the standard operating procedures, validation of sterilization and other operations should be conducted in advance through preliminary operations.

In addition, procedures for emergency operations should be established in advance.

3.3. Receiving of Cells and Tissues as Raw Materials

When receiving cells or tissues as raw materials, it must be confirmed that they are appropriate and meet the necessary standards according to the records listed in Chapter 2, 2.6-2.

3.4. Acceptance Testing and Examination of Reagents

For reagents used in the manufacturing process, standards shall be established, and acceptance tests and examinations shall be conducted.

3.5. Tests and Examinations of Products

Specifications shall be established and tests shall be conducted on the final products.
Specifications shall also be established and tests shall be conducted on products in the manufacturing process as necessary.

3.6. Elimination of Risk of Contamination by Bacteria, Fungi, Viruses, etc.

The risk of contamination by bacteria, fungi, viruses shall be eliminated by combining the following measures as appropriate depending on the characteristics of the products.

1. Confirmation of donor screening records at the time of receiving cells or tissues as raw materials.
2. Prevention of contamination in the manufacturing process.
3. Testing at each process of manufacturing.
4. Implementation of inactivation/removal methods using validated methods

3.7. Quarantine, Shipping and Delivery

1. Quarantine

   No such product shall be shipped without special reasons until the donor screening listed in Chapter 2, 2.4 and the product testing listed in Chapter 3, 3.5 have been completed for each donor and the eligibility of the product has been clarified.

   In the case of storing products prior to shipment until donor screening and product testing are completed, measures shall be taken to ensure that such products are not improperly shipped or manipulated by distinguishing them from cells or tissues used as raw materials prior to manufacturing and other products that can be shipped, by labeling, segregation of storage areas.
2. Shipping

   For each product, the name of the medical institution to which the product is to be shipped, the

date of shipment should be made clear.

3. Delivery

   During delivery, measures necessary to maintain product quality, such as temperature control, shall be taken.

3.8. Records of the Manufacturing Process

1. Records of each operation, tests conducted in the manufacturing process, as well as records of shipping and delivery, shall be prepared.
2. For each final product, the records listed in Chapter 2, 2.6 regarding the cells or tissues used as raw materials, the manufacturing records in 1, the test records, and the shipping and delivery records should be made available for confirmation.
3. The records listed in 2 should be kept at least 10 years after the product expiration date in principle.

3.9. Reflection of the Latest Technology

Manufacturing processes and tests shall be reviewed as necessary to reflect the latest knowledge and technologies.

Chapter 4: Personnel, Organization and Management System

4.1. Personnel and Organization

(1) Collection, storage, each operation in the manufacturing process, and tests of cells or tissues shall be conducted under the control and responsibility of persons with appropriate specialized knowledge, skills and experience in cell handling, cell culture technology or pharmaceutical manufacturing technology.

(2) Manufacturers, etc. should appoint a person in charge and have him/her manage information on personal information and safety of donors and patients obtained in the manufacture, import and sale of drugs containing cells or tissue, in order to handle such information appropriately.

(3) Prohibit entry into the facility by persons engaged in handling microorganisms or viruses that may infect or contaminate cells immediately before the collection and processing of cells or tissues, and by persons who may have undesirable effects on cell safety and purity.

4.2. Education and Training

Before the start of manufacturing operations, the following education and training are to be provided to manufacturing personnel to familiarize them with this Basic Concepts. Education and training shall be conducted on a regular basis.

1. Knowledge of the product
2. Knowledge and skills for safe handling of cells and tissues using in manufacturing
3. Knowledge and skills related to facilities and equipment
4. Knowledge and skills related to the safety of the manufacturing process
5. Knowledge and skills related to measures to be taken in the event of an accident

4.3. Health Management

1. Manufacturers shall conduct periodic medical examinations of manufacturing personnel and shall not allow persons who are not suitable for handling drugs containing cells or tissue to engage in manufacturing operations.
2. Manufacturers shall consider measures to prevent and treat infection in the work zone in advance when manufacturing drugs containing cells or tissue.
3. Manufacturers are to immediately conduct medical examinations of manufacturing personnel and take appropriate measures in the event that a threat of infection arises in the work zone.
   If necessary, the manufacturers should obtain the consent of the manufacturing personnel prior to engaging in manufacturing, collect serum samples in advance, and store them for an appropriate period during the period the worker is engaged in manufacturing and after the day the worker finishes manufacturing, or store the product in place of the serum.
4. When conducting medical examinations of manufacturing personnel, collecting and storing sera, consideration must be given to the human rights of the manufacturing personnel, including the protection of personal information.

Chapter 5: Measures to Ensure Safety at the Usage

5.1. Provision of Product Information

Manufacturers, etc. must appropriately provide medical institutions, physicians, and other healthcare professionals with information on the product, including the results of donor screening, tests of the final product, and serial or lot numbers.

5.2. Explanation and Consent

Persons who will apply drugs containing cells or tissue to patients must provide patients with sufficient explanation of the anticipated medical benefits and risks, management of patient records as described in 5.3 and 5.4, protection of personal information, and obtain their consent in advance of application.

5.3. Preservation of Patient Samples

In order to clarify whether or not a new infectious disease is caused by drugs containing cells or tissue in the event that a patient to whom drugs containing cells or tissue has been applied develops a new infectious disease in the future, manufacturers, etc. should store the final product for an appropriate period and, to the extent possible. In addition, the manufactures, etc. should preserve samples such as serum before application and records of pre- and post-application conditions related to infectious diseases of patients for the period necessary for the product, with the cooperation of medical institutions.

5.4. Obtaining Patient Information

1. Manufacturers, etc. of drugs containing cells or tissue should take appropriate measures so that information can be obtained when the adverse events, such as the onset of infectious diseases, occurs in patients and so that the health status of patients to whom the product is applied can be ascertained when a problem occurs with the product.
2. Manufacturers, etc. of drugs containing cells or tissue should explain in advance the measures listed in 1 to physicians and other medical personnel who handle drugs containing cells or tissue and obtain their agreement to cooperate in providing and storing the information. The measures listed in 1 may be implemented with the cooperation of medical institutions through prior agreement with them, for example, by describing the contents of the applied product, identification code, or product number in medical records.

Chapter 6: Protection of Personal Information

Persons who collect cells or tissues, members of the ethics committee, and persons who handle drugs containing cells or tissue must not divulge personal information about donors or patients obtained in the collection of cells or tissues or in the handling of such drugs containing cells or tissue. The confidentiality continues even after leaving these duties.

Chapter 7: Review

This Basic Concepts shall be reviewed as necessary, taking into account advances in science and technology, changes in social conditions related to the handling of cells and tissues, and other factors.