

GUIDELINE ON THE SAFETY, STORAGE, AND APPLICATION OF HUMAN TISSUE IN MEDICAL PRACTICE

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Consent to retrieval of human tissue from a deceased donor (sample format)

Reference

“Regulation of the safety and quality in medical products manufactured from human/animal derived materials” (abstract)

The Pharmaceutical and Medical Safety Bureau No. 1314, (26 December 2000)

Ministry of Health and Welfare (former body of the Ministry of Health, Labour and Welfare)

Japanese Society of Tissue Transplantation (JSTT)
6-20-2 Shinkawa, Mitaka City, Tokyo
181-8611 Japan
Tel: +81-422-40-7227
Fax: +81-422-40-7226
Website: <http://www.jstt.org/>
E-mail: info@jstt.org

I. INTRODUCTION

In Japan, the following tissues or organs, retrieved from a deceased donor, have been subject to clinical tissue transplantation, and research/study for medical application, under a spontaneous and autonomous regulating system of each medical institution.

They are: 1) skin, 2) cardiac valves 3) great/peripheral vessels 4) bones, ligament, 5) pancreatic islet cell 6) trachea, bronchi, and 7) cornea/sclera.

The retrieval, storage and application of the tissues and/or organs are conducted with the approval of the ethical committee or its equivalent body of each institution and with the donor party's informed consent. In order to obtain consent, the physician in charge of either recovery team physician or coordinator to give information and explanation to the donor's next-of-kin. Procured human tissue is usually frozen with the vapor phase of liquid nitrogen or deep freeze for storage (skin, cardiac valves, pancreatic islet cell, trachea and bronchi), which shall be categorized as minimally manipulated tissue as it does not include any cell engineering techniques, such as cell proliferation or DNA manipulation or transfection of the cells: Tissues of this type shall employ no further processing than cutting or segregation of tissue, separation of certain types of cells, processing with antibiotic agent, cleansing, sterilizing with gamma ray, etc., freezing, and thawing.

The safety standard of retrieval of the donor tissues and obtaining safety in the preserving process were independently regulated by each institution. On 26 December 2000, the Pharmaceutical Safety Bureau of the former MHW (the former body of MHLW-Ministry of Health, Labour and Welfare) issued notification No. 1314 of "Obtaining safety and quality in human resource products." (Please refer to Reference 1) This notification has been issued to establish a safety standard for manufacturers and companies who deal with medical products made from human/animal derived materials. Whereas JSTT is not a company or a manufacturer, it has also acknowledged that it should also comply with the safety standard presented therein, with exemption of the remarks on 'the donor tissues'. Those who take part in retrieval and transplantation with minimally manufactured human tissues are required to meet the standards and regulations stated in the following sections, and are expected to perform medical practice with high quality and medical safety.

II. RETRIEVAL OF HUMAN TISSUE

A. Legal Environment

All donation of human tissue is performed under the complete freewill of the donor, or by that of his/her next-of-kin if donated after the donor's death. Although there is no existing law regulating the retrieval of human tissue from a deceased donor for study or medical practice purpose, there is a guideline stated in the Organ Transplant Law implemented on 16 October 1997, providing as follows:

Article 11.2 "Handling of organs not regulated by the act"

The retrieval of an organ, which is not regulated by the existing act or the implementing regulation, from a deceased donor (including a brain-death donor) for the purpose of transplantation is prohibited.

Article 11.6 “Handling of tissues for transplantation”

While the act regulates transplantation of organs, it does not include tissues, such as skin, vessel, cardiac valves, bones, etc. Although there is no existing act or implementing regulation for tissues, the donation and transplantation of tissues is permitted when it is consented by the donor and/or by his/her next-of-kin, and where the practice is recognized as medically and socially appropriate. Therefore, consent of the donor and his/her next-of-kin shall be the minimum requirement required for retrieval of human tissue. The next-of-kin should be given sufficient information about what kind of tissue(s) would be retrieved, and for what kind of purpose it would be donated, etc. Obtaining written consent from the next-of-kin, after providing such information is appropriate as due process.

According to the guideline mentioned above, it is prohibited to retrieve an organ from a deceased donor if that particular organ is not controlled under the law. However, the law only controls the transplantation of organs, and is not applicable for tissues. The donation of tissue is therefore acceptable when it is conducted as a medical practice under the consent of the donor and his/her next-of-kin, and where the practice is recognized as medically and socially appropriate, with written consent of the next-of-kin who has been well informed and agreed about the kind of tissue to donate, and the purpose of the donation.

Tissues are usually recovered from a deceased donor after obtaining written consent. In some cases, tissues are donated along with other organs. For instance, there are cases such as the following:

1. Where the donor has given an explicit written consent to the donation of tissues (sections for ‘others’ in the donor card) as well as organs, and his/her next-of-kin has not objected to the donation, tissue may be retrieved from a legally brain-dead donor along with organs.
2. Even though the wishes of the donor toward donation may not have been made clear during his/her life, if the donor’s next-of-kin has given written consent for donation, tissue may be retrieved from the deceased donor, along with eyes or kidneys.

When the coordinator of JOTN (Japan Organ Transplant Network) provides information to the next-of-kin and obtains consent for the donation of organs and tissues, the organs are recovered by the organ retrieval team and JOTN would be called to notify a tissue recovery team from the tissue bank. In the case when regular procedures are to be followed (i.e. JOTN takes part in the process of giving information for obtaining consent to the donation of tissues as well as kidneys), and with proper consent, tissues may be recovered.

3. Donation of tissues from a donor who is not subject to organ donation. For the non-clinical brain dead donor cases, where there is consent obtained from the donor’s next-of-kin, it is possible to recover tissue with due consideration of the cause and the time of death, and checking if the donor meets the requirements stated below. Especially when the donor wished to donate corneas (eye balls), or a pathological autopsy is to be performed, donation of

other tissues may be allowed if the written consent is simultaneously obtained, and the donor meets the criteria for eligibility.

B. Compulsory Approval from the Ethical Committee

While there is no specific law that regulates the practice of tissue transplantation currently, it is desirable that the guideline for such practice follows the provisions and the requirements incorporated in the Notification No. 1314 issued by the Pharmaceutical and Medical Safety Bureau of former MHW on 26 December 2000: “Regulation of safety and quality in medical products manufactured from human/animal derived materials” (Please refer to Reference 1) Accordingly, having granted informed consent from the donor’s next-of-kin, it is necessary, firstly to get a formal approval from an internal ethical committee or an equivalent supervising body of the hospital or the institute concerned to procure and donate tissue. Equally, concerning the preserving tissues or performing a transplant operation with human tissue, it is essential to obtain formal approval from the internal ethical committee or a relevant body at the institute concerned.

C. Informed Consent (for tissue donation)

1. Obtaining informed consent (please refer to Appendix 1)
The written informed consent of the donor party (the donor, his/her immediate family members and next-of-kin) is the vital basis for retrieval, storage, application (clinically or academically), and/or disposal of human tissue. It has been conventional that the doctor in charge of the donor gives the donor party the information of tissue donation. In many cases, the same doctor performs the transplant operation. Although, there is no legal restriction existing to regulate the way to obtain consent, it is desirable to collect the signature of a witness (a nurse, etc.) simultaneously. Moreover, it is recommended to obtain informed consent from the donor party by a coordinator from a third party, such as JOTN. The person who actually gives the donor party information is required to sign the informed consent to prove his/her identity. At the same time, the donor party is also required to sign the consent form in order to clarify the will and intention of the party. Copies of the informed consent are to be prepared for the donor’s family, the facility and/or institute of tissue distribution, storage and transplantation. Copies of consent must be kept at each facility or institute for 20 years.
2. Notes on the contents of informed consent
It is necessary that the form of informed consent clearly indicate specification of the tissue to be donated. For tissue, which can be procured from wide and/or various areas of the human body, such as skin or vessel, it is also required to specify the retrieving site and the size, scale or volume of tissue to be procured in detail. These specifications are important aspects shown on the form of consent presented to the donor party on giving information.
3. Clarification of cases where tissue may not be used for transplantation – or may be applied to study or disposal
The primary application purpose of human tissue is for transplantation.

However, due to contamination and/or other factors, etc., there are cases when the donated tissue may not be appropriate for clinical use. In such cases tissue may be applied for research purposes. Thus, the form of consent should clearly state that when donated tissue did not fulfill the requirements for transplantation, it would be either applied for another purpose, such as research, or might be discarded.

III. REGULATION OF THE SAFETY OF TISSUES FOR TRANSPLANTATION

As of 26 December 2000, a formal notification namely, “Regulation of safety and quality in medical products manufactured from human/animal derived materials” (the Pharmaceutical and Medical Safety Bureau of MHW, No. 1314) was issued. (Reference 1) The chief of the Medical Safety Bureau issued this notification to the governor of each prefecture in Japan. The notification is intended for the manufacturers or companies, which deal with products made from human/animal derived materials. Yet, the contents of the notification should be extended to organizations with human tissue banking and/or storage functions. JSTT, too, considers that a tissue bank should operate in compliance with the principles presented in that notification for Regulation of the Safety Standard. Review of the notification applied to the tissue banking system, ‘manufacturers’ is the equivalent of tissue banks, which are responsible for maintaining the safety of tissues distributed to transplant facilities, and ‘manufacturing process’ is the human tissue preservation process. Even though the entire process, from retrieval, preservation through to application, is done internally and completed within a single institute, the required biosafety standard is the same as where tissues are distributed to/from external institutes.

When preserved human tissue is requested for clinical practice, it is extremely important to review the risks of disease transmission. A multi-strata approach must be taken to donor/tissue suitability:

1. Selection of donor (donor screening)
2. Prevention of contamination in tissue processing, and appropriate review of microbial contamination.
3. Tests and examination at each step of processing and application
4. Sterilization of tissues by validated methods, if required.
5. Keeping the records for 20 years

IV. CRITERIA FOR DONOR SCREENING

When a specific disease or state is observed in a donor, retrieval or transplant of tissue from the donor must not be permitted. It is necessary to conduct inspection and palpation of the donor, as detailed as possible. Interview of the donor’s next-of-kin and studying the donor’s medical records are also required.

The results of a pathological autopsy, if performed, must be reviewed. For all tests performed, conduct the most current methodology. Criteria and methods of tests or examinations must be always updated at a tissue bank, in accordance with technical and scientific advancements, and new findings in infectious diseases. (It is desirable to involve experts from related academic associations in the process of updating the criteria or collecting/evaluating information on infectious diseases, etc.)

In accordance with the principle presented in the above notification of the Pharmaceutical and Medical Safety Bureau of MHLW, retrieval of tissue is prohibited when a patient or donor corresponds to any of the following:

<Exclusion criteria of tissue donors in general>

- Death from unknown causes
- Documented cases of sepsis or other systemic infectious diseases
- CJD (vCJD) or its suspect of infection (see Note 1)
- Malignancy (as for primary brain tumours or solid tumours treated more than 5 years ago, and diagnosed to be cured, judgement may be given by the physicians to procure the tissue)
- Hematologic malignancies, such as leukaemia or malignant lymphomas
- Severe metabolic or endocrine disorders. Auto-immune disorders such as haematological diseases or collagen disease
- Syphilis positive (see Note 2)
- Hepatitis (HBV positive, HCV positive)
- AIDS (HIV positive)
- Adult T-cell Leukaemia (ATL), HTLV-1 positive
- Parvovirus B19 positive (see Note 3)
- West Nile Virus positive (see Note 4)
- SARS (see Note 5)
- Rabies (see Note 6)
- Other patient/donor who corresponds to exclusion criteria set for each tissue

Patients or donors must be negative in interviews and tests (serodiagnosis or NAT) for all these infections and diseases listed above. Where necessary, a patient or donor is to be tested for negative infection of cytomegalovirus and EB virus.

Note 1

As of June 2001, to avoid the risk of vCJD infection, it has been temporarily decided not to receive tissue from a donor with any medical history listed below. This provisional arrangement will be continued until new findings are brought forth or amendment in existing regulation is completed.

1. Dementia or other central nervous system manifestation of unknown causes, shown as a symptom of CJD
2. Family history of CJD or similar conditions
3. History of treatment with human derived growth hormone
4. History of cornea transplantation
5. History of dura mater implantation
6. Investigation in the record of overseas travel: lived cumulatively 6 months or more after 1980 in European nations, such as UK, Ireland, Switzerland, Spain, Germany, France, Portugal, the Netherlands, Belgium, Italy, etc. As a temporary precautionary measure, if patient or donor had such travel/residence record, his/her tissue should not be procured or donated. Tissue donation from a person who stayed a day in UK is prohibited, as of 2004.

Note 2

Usually, syphilis testing is carried out by combining the STS method and the TP antigen method.

1. STS method (nonspecific antigen reaction) is carried out by the glass plate method, the PRP method, other methods, etc. By the STS method, when the antigen value is negative in less than 1 time, it is necessary to run a more sensitive test.
2. TP antigen method (specific antigen reaction) – less than 80 times of the TPHA method or less than 20 times of the FTA-ABS method is considered negative.

For the STS method, less than X1 of antigen is negative

Note 3

According to the notification of the Pharmaceutical and Medical Safety Bureau of MHW, Parvovirus B19 must be equally measured in accordance with hepatitis virus (HB, HCV) or HIV. However, in most cases, infection of Parvovirus B19 occurs in one's childhood. Therefore, there must be a certain standard to prove positive of this virus. Additionally, Parvovirus B19 has a high affinity for erythrocytes and it is unknown how much of it can exist in the tissue.

Note 4

Centers for Disease Control and Prevention (CDC) states in its official report that West Nile Virus is transmitted via blood transfusion or organ transplant. In accordance with this report, as of November 2002, a temporary safety measure has been taken: i.e., prior to donation, a thorough interview is required, when the donor has a history of travel one month prior to donation to the areas affected by West Nile Virus, including the US.

Note 5

1. Where the donor has a history of travel to areas with suspicious cases of 'regional transmission' of SARS virus by the WHO's report, in the 3 weeks prior to the donation, tissues of that donor must not be used for transplantation.
2. Strengthened interview is required to screen if the donor corresponds with the "probable SARS case" (Notification No. 0508001 TB and Infectious Disease Dept. of the Health Bureau, 8 May 2003). Should the donor fit the case, tissues or organs of the donor must not be used until 3 months have passed after a complete recovery confirmed and the course of treatment finished.
3. Strengthened interview is required to screen if the donor corresponds with the "suspected SARS case". Should the donor fit the case, tissues or organs of the donor must not be used until 1 month has passed after a complete recovery has been confirmed and the course of treatment finished.
4. Those who nursed, attended or took care of a person who fits in case (2) or (3) in the 3 weeks prior to donation should not donate tissues or organs.

Note 6

1. If the donor corresponds with the "suspected Rabies case", his/her tissue should not be procured or donated.
2. Investigation the history of overseas travel within 7 years past, and the experience of biting by mammalia. Should the donor fit the case, the recipients must be explained about Rabies and the risk of infection.
3. When tissue of the donor fit in case (2) was transplanted, should urge a surgeon to

follow up the recipient.

V. PROCESSING AND PRESERVING OF HUMAN TISSUES

A. Processing and Storage of Human Tissue

A tissue bank must prepare an institutional Standard Operating Procedures (SOP) for processing and preserving of human tissues. Complying with the SOP, a bank must prevent contamination and perform appropriate microbial tests. The safety in the process of procured human tissues and its efficacy for transplantation must be confirmed.

1. Secure the safety in equipments, tools, agents, aerious and aqueous environments for processing and preserving human tissue.
2. Prevent contamination by maintaining an appropriate environment when processing or preserving procured tissue: i.e. using sterilized tools or working inside a sterilized room. At the same time, operators must be also protected from possible infections through tissues by wearing protective gowns.
3. Using a part of the procured tissue, culture tests for bacteria and fungus must be done.
4. Microbial inactivation, such as disinfection or sterilization, must be performed in processing the procured human tissue. Culture tests or examinations for bacteria and fungus are also required at each step of the processing procedure.
5. Maintain the cleanliness standard of the room for processing and preserving of human tissue. The safety for operators must be simultaneously kept. Regular checking of quality of environment is required.
6. Procured tissues should be withheld until all test results of microbial, fungus and acid-fast bacteria (AFB) are collected. Before collection and review of the results, tissue must not be applied to transplantation. Fresh cornea, skin and pancreatic β -islet cells, etc., are exempt from this measure.
7. All the records collected from above, must be kept and archived. A tissue bank should establish SOP for processing and preserving human tissues. A record describing the procedures and the state of processing and preserving must be prepared and maintained. Regular internal review of such records is required to evaluate the validity of the whole process. When necessary, an external evaluation by external organization should be also employed.
8. Adverse reactions in human tissue transplant require the JSTT be contacted immediately.

It is desirable to report the case to the Organ Transplant Office of the MHLW, too, as a cooperation of medical risk control. (Notification No. 0520002 issued by the Organ Transplantation Dept, Diseases Control Division, the Health Bureau of MHLW on 20 May 2002)

B. Prevention of Contamination in Processing and Storage

Directions to follow to prevent contamination and ensure microbial clearance in processing and preserving of human tissues procured from an eligible donor are shown below.

1. Swabs or biopsies must be taken from procured tissues and cultured for

bacteria (including tbc mycobacterium) and fungus screening tests. Screening should include gram-positive/negative bacteria, anaerobic/aerobic organisms (acid fast bacteria), chlamydia and mycoplasma.

2. Tissue processing should be operated inside a clean bench.
3. After performing disinfection with prepared antibiotics, repeat culture tests of bacteria and fungi. Cryopreservation procedure follows this step. Previously, 10% fetal bovine serum (FBS) was used as preserving solution, however, until its suspected relations to BSE is cleared, use of FBS should be suspended. Reports show that no substantial effect to the quality of cryopreserved tissue was recognized without the use of FBS.
4. When cryopreserved tissue is thawed for use, the preservation solution and remaining part of the tissue must be taken and cultured for bacteria (including tbc) and fungi screening tests.
5. All the records collected from above (1-4) must be kept in an appropriate manner and archived for 20 years according to the revision of the Pharmaceutical Law, 31 July 2003.

Note 1

In case a weak positive reaction to resident microbe is observed at tests of (1), and then found negative with tests mentioned in (3), judgement of tissue eligibility must be made after thorough checking.

Note 2

Where results of tests mentioned in (3) turned bacteria/fungus positive, the tissue must not be applied to clinical purpose and may be used for research purposes based upon the consent form obtained from the donor party.

Note 3

These directions do not apply to the cases of fresh unpreserved cornea for transplantation use, skin and pancreatic β -islet cells.

C. Human Tissue Distribution for Clinical Application at a Transplant Facility

1. When a tissue bank distributes human tissues to a transplant facility, the distribution must be conducted fairly in accordance with an explicitly written procedure. Selection of a recipient must be done carefully based on the idea of the equality of opportunity.
2. A tissue bank must report the criteria, procedures, and results of donor screening tests, and provide information about processing of the tissue to a transplant facility.
3. All personal data must be secured to protect donor and recipient confidentiality and anonymity while maintaining traceability. Such data must be kept at the tissue bank for at least 20 years.
4. A transplant facility must obtain an informed consent from the recipient party prior to the transplantation. To obtain such consent, physicians of the transplant facility should give sufficient information to the recipient party on the safety, efficacy and potential risks in human tissue transplantation.
5. On performing transplantation, the transplant facility must keep the record of the source bank name, ID number of applied human tissue, etc., and establish a system capable of tracking back by appointing a data control manager when necessary.
6. Those who are engaged in human tissue banking and transplantation must strictly protect and keep confidential all personal data of the recipient and other information, which may lead to identification of the recipient or which the recipient party wishes to withhold. Such data or information should not be disclosed to a third party. The personnel in charge of controlling and managing such confidential data is necessary as described in (IV) of "JSTT Ethical Guidelines for Application of Human Tissue to Medical Practice." Such a data control manager should not be a staff member but should be the director or head of the administrative department or the transplant institution.
7. A tissue bank must not receive, seek, or be assured any financial reward from a transplant facility or a patient over human tissue distribution. However, the reasonable amount of actual expenses for activities needed as a non-profit organization such as travel, communication, coordination, retrieval, storage, and transportation are not involved in or not considered to be financial reward.

Appendix

Consent to Retrieval of Human Tissue from a Deceased Donor (Sample Format)

Informed Consent Form (Sample)

Name (of the person to whom this letter is addressed)
Title
Name of Organization or Hospital

We, all family member(s) of under mentioned patient, hereby confirm that we have been informed of and understand the significance, procedures, testing requirements, and processing relating to tissue donation. On this basis, we agree to donate the following tissues under the following conditions for tissue transplantation after the death of the patient.

Name of Patient:
Sex: Male / Female
Date of Birth:
Address:

1. Tissue for donation (Please circle the item(s) you agree to donate. If cross-marked, that item will be excluded from the donation list.)
 - a. Skin (Principle donating site is specified in the attached figure)
 - b. Cardiac valves (Whole heart will be retrieved but the parts other than the valves may be returned to donor's body on request)
 - c. Great vessels, peripheral vessels (Principle donating site is specified in the attached figure)
 - d. Bones, ligaments (Principle donating site is specified in the attached figure)
 - e. -islet cell (Pancreas will be retrieved)
 - f. Trachea, bronchi
 - g. Others
2. Blood sample (about 10 cc) for testing
3. Prior to retrieval, this consent can be withdrawn at any time.
4. In case the donated tissue(s) turned out to be not suitable for clinical transplantation, the tissue(s) will be [cremated, applied to research and study with approval of the ethical committee, or other]

Time Day Month Year

Following (a) – (c) must be auto scripted respectively

- a) Name of representative of family members:
Relation to the patient
Address
Telephone number

- b) Name of person who provided information and explanation
Title
Name of organization
- c) Name of witness
Title
Name of organization

NOTES

1. The word 'death' used in the term 'after the death of patient' means after cardiac arrest. Retrieval of tissues at brain death is only allowed where the following two requirements are fulfilled in compliance with the Organ Transplant Law: Firstly, the donor gave an explicit written consent, during his/her life, of donation of tissues upon brain death, and showed acceptance of the review of brain-death tests. Secondly, donor's next-of-kin did not object to the brain death tests, and the judgement given subsequently.
2. It is desirable to indicate the amount of time required to retrieve tissues on the Informed Consent Form.
3. It is desirable to describe the way of restoring the donor after the retrieval.
4. It is preferable to have a coordinator to provide information to the donor party. When a doctor belonging to the donor (or recipient) party gives information, it is desirable to have a witness as the third party (i.e. a nurse), and to obtain a signature of the witness in the consent.

Reference

Regulation of the safety and quality in medical products manufactured from human/animal derived material”

(No. 1314, The Pharmaceutical Safety Bureau of former MHW)

26 December 2000

Principles of Good Tissue Practice (GTP) Abstract

Section 1. General Provisions

Part 1. Purpose

To prevent the introduction, transmission, and spread of communicable disease through the use of cellular and tissue-based products, it is required that the products do not contain communicable disease agents, and that the products do not become contaminated during manufacturing. Subsequently, it is necessary to prevent contamination during manufacturing, handling and use of the product. The regulation requires consistent delineating material collection, manufacturing and use of the products. The purpose of this guidance is to establish general requirements to handle cells and tissues in order to assure the quality and safety of cellular and tissue-based products in conjunction with manufacturing processes as well as to secure the scientific and ethical rationale of the handling operations.

If procedures other than this document are taken, it is necessary to explain to the authority the necessity and the justification of the deviation from the quality and safety assurance point of view, showing the basis.

The provision delineated in this document is applied to the dossiers of both cellular and tissue-based product application and investigating drug application.

Part 2. General Principle

The use of cellular and tissue-based products should be confined to the medical treatments where the clinical advantage over the other products/treatments is expected, because the potential risk of the transmission of the communicable disease agents derived from them is not completely ruled out.

Part 3. Definition

1. Cellular and tissue-based product - a biological drug or medical devices containing or consisting of human or animal cells or tissues.
2. Donor - a person who provides the source materials of cells or tissue for a cellular or tissue-based product. The cases of organs donated after the brain death, complying with the Organ Transplant Law (Law No. 104, 1997) are exempted from category of definition herein.
3. Donor animal - an animal that provides the source materials of cells or tissue for a

- cellular or tissue-based product.
4. Attorney - a person who acts on behalf of donor to participate in the interview and the informed consent. If the donor is alive but unable to participate in the interview, the attorney is supposed to be a person who exercises the donor's parental authority, donor's spouse, or donor's guardian. If the donor is not alive, the attorney is supposed to be the bereaved family.
 5. Donor screening - to determine, by diagnosis and tests, whether the donor of cells or tissues is compatible with criteria of donating the materials for the cellular and tissue-based product.
 6. Window period -a period when the infectious agent or the antibody against it could not be detected in the early stage of infection.
 7. Operating area - an area where cellular and tissue-based products are directly handled and manufactured.

Section 2. Suitability for Source Material (Cell and Tissue) Collection

Part 1. Institution for Source Material Collection

Cells and tissues shall be collected in the medical institution, which meets the requirements described below, or meets the requirements equivalent to those described below.

1. Necessary hygienic environment for collecting and preserving cells or tissues shall be well controlled and the knowledgeable, experienced and competent staff shall be instituted.
2. The ethical committee shall be instituted within the institution to discuss the suitability for practices of cells or tissues collection in case the donor is human.
3. The ethical committee should meet these criteria:
 - a. The committee is competent to discuss the suitability for the practices of cells or tissues collection from a scientific and ethical point of view.
 - b. There are established official rules applying to the operation of committee.
 - c. The committee is comprised of respective experts from ethical, legal and scientific fields and it must also include a member of the public.
 - d. The proportion of members from each field stated above must be well balanced in the committee.
 - e. The head of the institute, any staff who will be handling the cells and tissues, and any person who has a close relationship to the sponsor should not participate in the discussion and the vote.
 - f. A valid session of the committee requires more than one respective member from ethical, legal fields, and the public participating.
4. The manufacturers processing/handling of the collected human cells or tissues shall institute the ethical, corresponding to the article 2 of the above committee, and shall discuss and investigate the suitability for processing/handling of cells or tissues from a scientific and ethical point of view.

Part 2. Donor Acceptance for Collection (Informed Consent)

1. Written Consent
The person intending to collect cells or tissues shall explain by documentation to the donor-to-be the purpose of utilizing cells or tissues, privacy, security, and other things

concerned with collection of cells or tissues, and shall obtain the consent by documentation in advance. The person shall also explain that the donor has the right to exercise rejection and withdrawal and that there will be no disadvantage caused by doing so.

2. The case where obtaining written consent from the donor is difficult
When the donor is unable to consent, the person intending to collect the materials should obtain the attorney's consent.
 - a. The collection of cells/tissue from the donor has rational reasons, from quality and safety assurance point of view as medical products.
 - b. It must be proved that the attorney is the best person to represent the well-being of the donor. Where consent for donation is given by the attorney, the relationship between the donor must be recorded and kept with the letter of consent.
 - c. Even in the case as above, the best possible effort should be made to pass necessary information to the donor, and try to obtain the first-person consent.
 - d. The ethical and scientific correctness of cells/tissue collection from the donor has been reviewed, discussed and approved by the ethical committee of the institution of source material collection.
3. On receiving cells/tissue donation from a deceased donor, the information about the donation must be provided to the donor's bereaved family as described in 1 and 2, for obtaining the consent. Such case is feasible only when the deceased donor did not object, during his/her life, to donating cells/tissue after death.
4. Application of cells/tissue retrieved during surgical operation, etc. When applying cells/tissue retrieved during a surgical operation, etc., obtaining consent, as described above is necessary. In such case, the priority of the surgical operation must not be shifted for the sake of cells/tissue collection.

Part 3. Donation on Non-profit Basis

Donation of human cells/tissue should be done on non-profit basis. Yet, some actual expenditure, which the donor party had to cover in order to donate cells/tissue, such as travel expenses, etc., shall be compensated through approval of the ethical committee.

Part 4. Donor Suitability Criteria and Donor Screening

1. Where the donor is human
 - a. When collecting tissues or cells, in order to verify the compatibility with donor suitability criteria, the donor shall be diagnosed for all or a part of the listed risk factors below relevant to communicable disease agents where appropriate. Donor screening shall not necessarily be performed when autologous tissues or cells are used.

The possibility of the B type hepatitis (HBV), C type hepatitis (HBC), infection of human immunodeficiency virus (HIV), adult T-cell leukaemia, and infection of Parvovirus B19 should be evaluated by diagnosis and tests. (Serodiagnosis or NAT) The possibility of the infection of cytomegalovirus and EB virus should be evaluated by diagnosis and tests where appropriate. Additionally, it is required to examine the medical history and conduct interview about the diseases shown below, and to review the history of blood transfusion, and of transplantation to

determine donor suitability.

- Infectious disease of bacteria including *Treponema pallidum*, *Chlamydia trachomatis*, *Neisseria gonorrhoea*, and *Mycobacterium tuberculosis* or tuberculosis bacillus.
 - Documented sepsis or the suspicion of it
 - Malignant tumor
 - Serious metabolic and endocrine disease
 - Collagen disease and haematological disorder
 - Hepatic disease
 - Dementia (BSE or the suspicion of it)
- b. Testing shall be performed using most appropriate donor screening tests with reference to the highest possible scientific level at present. The parameter and test methods should be subject to changes in accordance with new findings of infectious diseases and the progress of science and technology.
- c. A new specimen shall be taken from the donor and retested for the evidence of infections within the appropriate time frame, depending on communicable disease agents and characteristics of test methods, due to possible window periods.
2. Where the donor is an animal

(This section is omitted)

Part 5. Proper Collection Handling Practice

1. The cells and tissues should be collected under the germfree condition to prevent contaminations. The status of collected cells and tissues shall be determined and identified by appropriate tests with respect to microbial and infectious disease agents and verify the absence of contamination of these agents at the time of collection. The parameter and test methods should be subject to changes in accordance with new findings of the infectious disease and the progress of science and technology.
2. When collecting cells and tissues from a deceased donor, the decency and respect for the donor must be maintained.

Part 6: Contents of Donor Suitability Record

1. Records shall be prepared with donor screening, compatibility with criteria receiving donor animals, practices of breeding donor animals and cells and tissues collection, and performed test of collected cells and tissues.
2. Record of cells and tissues as source materials for cellular or tissue-based product shall provide the records including institute of source material collection, the minutes of the committee, documentation of patient information provision and written informed consent, the date of collection, results of diagnosis on test determining donor suitability, results of acceptance of donor animal's tests, record of breeding donor animals, and practice collection. When appropriate, each manufacturer shall establish a method or system that enables collecting information of tardive communicable diseases' occurrence of donors for tracking.

3. In general, record specified in article 2 should be retained for at least 20 years after the expiration date of the cellular/tissue-based products. It is advised to retain samples of a part of collected cells and tissues within appropriate time frame, for verification of manufacturing process and the result of treatment, and for investigating the cause of communicable diseases in case a recipient is infected.

Section 3. Handling of Collected Materials during Production

Part 1. Quality Assurance System

1. A facility that performs any step in the production of cellular or tissue-based products shall establish and maintain consistent quality assurance system appropriate for product characteristics.
2. A manufacturer shall have the facility and equipment segregated into separate or defined areas for each operation of cellular and tissue-based product manufacturing, such as receipt/acceptance of source materials, manipulation, storage of intermediates and final products.
3. To prevent improper handling of mix-ups, contamination of transmissible agents, cells and tissues from more than one donor shall not be pooled during manufacturing.

Part 2. Standard Operating Procedure and Implementation

Manuals of standard operating procedures for each operation in production shall be documented. Operations such as sterilizing shall be validated by a pilot operation before making the manuals.

Part 3. Acceptance of Cells and Tissues as Source Material

The manufacturer of the cells and tissues as source material for manufacturing of the product shall verify the suitability by records as stipulated in Part 5 of Section 2.

Part 4. Acceptance of Reagents

The manufacturer shall establish an acceptance criteria for suitability of reagents used in the process of manufacturing and shall perform tests for suitability.

Part 5. Specification of the Final Products

Each manufacturer shall establish the criteria for the final product where appropriate, and perform the tests for suitability. Each manufacturer shall also establish the in-process criteria and perform the tests for suitability.

Part 6. Prevention of Contaminations from Bacteria/Fungus/Virus, etc.

The following measures should be appropriately combined according to each product, in order to prevent contaminations from bacteria/fungus/virus, etc.

1. Checking the results of donor screening tests performed on receiving tissue/cells
2. Employing prevention measures against contamination during the manufacturing process
3. Performing tests and examinations at each stage of the manufacturing process
4. Employing validated methods for bacteria/fungus/virus inactivation and elimination

Part 7. Quarantine, Shipping and Transportation

1. **Quarantine**
Without an exceptional reason, no products should be allowed to ship out before the completion of donor screening tests, as described in Section 2 Part 4, and quality assurance for end products, as described in Section 3 Part 5. Before the completion of those tests, products must be kept separated from source materials or the products ready for shipping, with clear indication in a designated area, in order to prevent operational errors, such as being shipped out or processed by mistake.
2. **Shipping**
Shipping information, such as the name of the transplant institution (the consignee) or date of shipment, etc., must be clearly and individually given to each product.
3. **Transportation**
Measures for quality preservation, such as controlling of temperature, etc., must be taken during the transportation.

Part 8. Record about the Manufacturing Process

1. Records must be prepared and kept about each operation taken under manufacturing process, tests, examinations, shipping, and transportation.
2. Each end product should bear records, which is available for reviewing, about source cells/tissue, as described in Section 2 Part 6, about manufacturing as described above 1 and also about tests/examinations, shipping, and transportation.
3. All the records listed in above 2 must be kept for at least 20 years after the expiry date of each product.

Part 9. Updating of the Operation

Manufacturing process and test methods must be appropriately updated in accordance with the technical advancement and the latest scientific knowledge.

Section 4: Staff Members, Organizational Structure and the Administrative Measures

Part 1. Staff Members and Organizational Structure

1. Retrieval, storage, manufacturing operations, tests and examinations must be performed under the control of appropriate personnel with sufficient knowledge, technique and experience in tissue/cell culturing or manufacturing of medical products, etc.
2. The manufacturer must appoint a manager for controlling the donors/recipients'

- personal data acquired in the process of manufacturing, import or distribution, and for administrating the safety assurance information of the products, etc.
3. Prior to the start of the Retrieval or processing of tissue/cells, it must be prohibited to allow entrance of anyone who has just handled infectious bacteria or virus or who may give an undesirable effect to the safety and quality of tissue/cells to the operating area.

Part 2. Education and Training

Prior to taking part in the manufacturing process, operators should first understand the contents of this guideline, and be given adequate opportunity to learn the following points, prior to taking part in the manufacturing process. Regular opportunities of education and training must be provided for such operators.

1. Knowledge of the products
2. Knowledge and technique of safe handling of cells and tissue as source materials
3. Knowledge and technique for proper use of manufacturing devices and equipment
4. Knowledge and technique to secure the safety in the manufacturing process
5. Knowledge and technique about necessary measures to be taken for accidents or mishaps

Part 3. Health Administrations

1. In order to avoid the risks of involving infected staff members in the manufacturing process, a manufacturer needs to provide regular health checkups for its staff members.
2. A manufacturer needs to prepare measures to prevent infections and to handle accidentally infected cases occurring within the operating area.
3. If an infected case should occur in the operating area, the manufacturer must immediately send its staff members for health checkups, and take appropriate measures subsequently. Where necessary, a manufacturer may procure serum from each of its manufacturing staff members under consent, and store it during the period that he/she takes part in the process, and possibly for a certain period of time after he/she left the post. Alternatively, samples of products may be stored, instead of serum of staff members, for the same period of time.
4. Human rights and the confidentiality of personal data of staff members must be adequately secured when a manufacturer provides health checkups, procures and stores serum samples of them.

Section 5: Safety Measure for Use of Products

Part 1. Providing Information on the Products

A manufacturer must appropriately provide information to the relevant medical institutions, physicians, etc., about the results of donor screening tests and the examinations performed on end products, as well as product identifying data such as the lot number and manufacturing serial numbers, etc.

Part 2. Informed Consent

Those who apply cells or tissue-based products must first obtain informed consent from the patient through providing sufficient information about clinical advantages, potential risks, and protection of personal data as described in the following Parts 3 and 4.

Part 3. Reserving Samples Taken from Patients

After the application of cells and tissue-based medical products, the manufacturer should preserve records and samples of the patient to prepare for a potential case of infection. Such records and samples to be retained are (1) a sample of end products to secure the traceability should the patient become infected, (2) serum and other tissue samples of the patient taken prior to application of the products, and (3) medical history or records of the patient about infections. Where available, samples and records of (2) (3) are encouraged to be collected and retained with cooperation of relevant medical institutions. Obtained records and samples should be stored for an appropriate period of time, according to the characteristics of each product, for future reference.

Part 4. Maintaining the Access for Relevant Patient Information

1. A manufacturer must ensure that it can obtain relevant information if a patient should develop symptoms of infections after the use of cells and tissue-based medical products, or that it can check the physical conditions of relevant patients when a defect should be found in a product.
2. In order to secure future cooperation, a manufacturer should explain the means or method to practice (1) to physicians and relevant medical institutions, and should obtain consent from them to keep and provide necessary information: e.g. In the medical records, physicians or medical institutions keep the identification code, serial number and the contents of the products used.

Section 6: Protection of Personal Data

Those who take part in the retrieval, the ethical committee, or handling of cells and tissue-based products, must keep the confidentiality of personal data of the donor and recipient party, which may be acquired through their duties. The responsibility of securing the confidentiality shall extend even after one leaves his/her post.

Section 7: Assessment of the Guideline

This guideline must be appropriately assessed and updated in accordance with the advancement of technology and changes of social conditions toward the applications of cells and tissue.