Japanese Society of Tissue Transplantation

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

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CONTENTS

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INTRODUCTION

Regarding the application of the tissues retrieved from deceased donors to the medical treatment, which has been practiced as a medical practice, the following tissues, in Japan, have been used for the clinical application or its research under the voluntary and self-management system of each medical institution.

1) skin, 2) cardiac valve, 3) great/peripheral vessel, 4) bone, ligament, 5) pancreatic islet, 6) trachea, bronchus, 7) cornea/sclera and 8) amniotic membrane.

The retrieval, storage and transplantation of these tissues are carried out with the approval of the ethical committee or a similar organization at each medical institution, and based on the informed consent of the donor party (donor himself/herself in the case of live donors, custodial parent or proxy in the case of minors, the bereaved family in the case of deceased donors).

Regarding storage, the cryopreservation method using liquid nitrogen and a deep freezer is the main method (skin, cardiac valve, pancreatic islets, trachea and bronchus), which shall be categorized as “minimally manipulated group” in terms of tissue engineering, as it is preserved without using cell engineering techniques such as proliferation and genetic manipulation of cells that compose tissues. Tissues of this type shall undergo no further processing than chopping or segregation of tissue, isolation of certain types of cells, processing with antibiotic agent, cleansing, sterilizing with gamma ray, freezing, and thawing.

In the past, safety standards for these medical practices and ensuring safety through the preservation process were left to voluntary facility management. On December 26, 2000, the Pharmaceutical Safety Bureau of the Ministry of Health and Welfare (MHW, current Ministry of Health, Labor and Welfare; MHLW) issued Notification No. 1314, “Ensuring the Quality and Safety of Pharmaceutical Products Manufactured from Human/Animal-Derived Materials” (Reference 1). Although this notification has been issued to establish a safety standard for manufacturers and companies that deal with pharmaceutical products made from human/animal-derived materials, the Japanese Society of Tissue Transplantation (JSTT) also recognizes that it is necessary to comply with this safety management standard. However, the section regarding "donor animals" in this notice is not included in the medical practice specified in this guideline. Those

engaged in transplant medicine using the above-mentioned minimally manipulated human tissue need to perform fair, transparent and reliable medical treatment in accordance with the following criteria.

This guideline was prepared by the Guideline Committee of the JSTT in 2002. This guideline presents the basic principles of the Society based on various laws, guidelines, medical knowledge and others regarding procurement and preservation of human tissues, donor criteria and other matters to ensure the safety in the tissue transplantation using human tissues.

Then in 2009, the "the Organ Transplant Law" was amended, and the "Regulation for Enforcement of the Organ Transplantation Law" and "Guidelines to Application of the Organ Transplantation Law" were also revised. Along with this, the legal requirements for donation of organs after death, medical requirements, consent procedures, procedures leading up to removal of organs, etc. have been changed.
And in 2014, the "Act on Securing the Safety of Regenerative Medicine", "Regulation for Enforcement of Act on Securing Safety of Regenerative Medicine" and "Order for Enforcement of the Act on Securing Safety of Regenerative Medicine " were enacted, and allogeneic pancreatic islets transplantation is now classified as Type 1 regenerative medicine (in the case of autologous islets transplantation, it corresponds to Type 3 regenerative medicine).

Additionally, emerging infectious diseases that may be transmitted by the tissue transplantation have also been reported, since the 1st edition of this guideline was published. And in 2010, the JSTT has established a system for diversion of tissues preserved in the tissue bank to research, "The Appropriate Use Review Committee", and formulated "Guideline on Tissue Utilization for Research" and "Guidance on Tissue Supply for Research". This guideline has been revised in order to respond to the above-mentioned changes in the situation inside and outside the country and new findings.

1. RECOVERY OF HUMAN TISSUE

1-1. Legal Environment

There is no law on tissue/cell retrieval from human donors for research and medical practice in Japan, but "Guidelines to Application of the Organ Transplantation Law" enforced on October 16, 1997 (Notification No. 1371 (partially revised May 1, 2012,

Notification No. 0426 No. 1)) stipulate as follows.:

Article 12.2 "Handling of organs not stipulated by the Law"
"For the purpose of organ transplantation, the recovery of organs not stipulated by the Law and Regulation for Enforcement of the Organ Transplantation Law from deceased donors (including brain-dead donors) shall not be carried out."

Article 14 "Matters concerning the handling of tissue transplantation"
"While the Law stipulates the transplantation of organs, it does not include tissues, such as skin, vessel, cardiac valve, bone, etc. Although there are no special laws and regulations for transplanting these tissues, it is usually acceptable when performed as a medical practice with the consent of the person himself/herself and/or by his/her next-of-kin, and when it is deemed appropriate from a medical point of view and social point of view, etc. Therefore, when recovering the tissue, it is at least necessary to obtain the consent of the bereaved related to the recovery of the tissue. And so after giving sufficient explanation about the type of the tissue to be recovered and its purpose, etc. to the bereaved, it is appropriate to obtain written consent as due process."

Article 12-2 of "Guidelines to Application of the Organ Transplantation Law" states that organs not stipulated in "the Organ Transplant Law" and "Regulation for Enforcement of the Organ Transplantation Law" cannot be removed from the corpse. However, the Law does not stipulate the tissue transplantation, but the organ transplantation. Based on the article 14 of "Guidelines to Application of the Organ Transplantation Law", if tissue transplantation is performed as a medical practice with the consent of the donor or the next-of-kin (donor himself/herself in the case of live donors, custodial parent or proxy in the case of minors, and the bereaved family in the case of deceased donors), it is clearly stated that the tissue can be provided with written consent after sufficient explanation about the type of tissues and its purpose.

Usually, the donation of tissues includes the case where the tissues are donated as well as organs after brain death or after cardiac death, the case where the tissues are donated alone after cardiac death, and the case where the tissues are donated from live donor (residual tissues at the time of surgery). The following cases can be considered for these;

1-1-1. In the following cases, the tissue can be removed after the organ is removed from the body of a person (including the legally certified brain-dead) with the written

consent of the family.

1-1-1-1 When the person indicates the intention to donate organs and tissues in writing and does not indicate the intention to refuse the brain death determination, and moreover the family does not refuse the donation of organs and tissues or the brain death determination, or there is no family (Law Article 6, Paragraph 1.1 and Paragraph 3.1),

1-1-1-2 When the person indicates the intention to donate organs and tissues in writing, or when does not indicate the intention to refuse these donation, and moreover does not indicate the intention to refuse the brain death determination, in addition when the family gives written consent for these donation and brain death determination (Law Article 6, Paragraph 1.2 and Paragraph 3.2),

1-1-2. When the person indicates in writing the intention to donate organs and tissues after cardiac death, or when the person's intention to donate organs and tissues is unknown, in addition when the family (the bereaved) gives the written consent of the donation of organs and tissues, tissues can be recovered after or at the time of the recovery of the kidneys and/or eyeballs.

If the person indicates the intention to refuse the brain death determination or organ donation but does not indicate the intention to refuse the tissue donation, or if the family refuses the brain death determination or organ donation but does not refuse the tissue donation, it is possible to donate tissues after the cardiac death with the written consent of the family.

1-1-3. When the person's intention to refuse the organ donation is indicated, when the consent of the family to donate organs cannot be obtained although the person's intention to donate organs is indicated or unknown, or when the person is not eligible for the organ donation due to medical reasons, and moreover when the living will to donate the tissue is indicated in writing, or unknown, only tissues can be removed after cardiac death with the written consent of the family (the bereaved) to donate tissues. In this case, pancreatic islets cannot be donated at this time.

1-1-4. Regarding the donation of tissues (skin, blood vessel, heart valve, bone/ligament, amniotic membrane, pancreatic islet, etc.) that are surgically removed during the surgical operation and medically discarded (the tissue to be discarded; called “residual

tissue"), if the person himself/herself agrees in writing after the sufficient explanation about the donation of residual tissues, it is possible to donate residual tissues for which consent has been obtained.

In the case of [1-1-1], when the transplant coordinator of the Japan Organ Transplant Network obtains the written consent of the brain death diagnosis and the organ removal from the family (the bereaved), it is possible to explain the donation of each tissue in cooperation with the tissue transplant coordinator.

In the case of [1-1-2], in the process of obtaining the consent for the donation of kidneys and/or eyeballs with the cooperation of the Japan Organ Transplant Network and/or the Eye Bank, each tissue bank cooperates to explain the donation of tissues at the same time, and tissues for which the written consent is obtained can be donated.

In the case of [1-1-3], that is, for tissue donation from a deceased donor that is not subject to organ donation, with the consent of the family (the bereaved), and considering the cause of death and the condition at the time of death, it is possible to donate tissues after cardiac death if the donor criteria of the tissue donation described later are met. In particular, if the deceased wishes to donate the cornea (eyeball) or if autopsy is permitted, the Eye Bank or the tissue transplant coordinator will explain the tissue donation at the same time and if the donor criteria are met and if the written consent is obtained, it will be possible to remove the cornea (eyeball).

In the case of [1-1-4], the patient safety should be the first priority. The excision should be the minimum necessary for the treatment of the patient, and the donation of the excised tissue should not affect the change of the extent of resection.

1-2. Necessity of Approval by the Ethical Committee

There is no legal requirement for the implementation of tissue transplantation, but it is desirable to maintain in accordance with the instructions in "Ensuring the Quality and Safety of Pharmaceutical Products Manufactured from Human/Animal-derived Materials" (Reference 1) issued by Pharmaceutical Safety Bureau of the former MHW on December 26, 2000 (Notification No. 1314). In other words, based on the informed consent with the donor and its family (described later), it is necessary to obtain the consent of the hospital director and the in-hospital consensus that provides the tissues

through the ethics committee at the hospital. However, the judgment regarding the suitability of tissue donation for each case is in accordance with the policy of each facility. Similarly, it is essential to obtain the approval from the ethics committee, etc. at each facility for the tissue preservation and the tissue transplant surgery.

1-3. Informed Consent (for tissue donation)

1-3-1. Obtaining informed consent

The informed consent with the donor family is the basis for tissue recovery, storage, utilization (transplantation or research) and disposal of human tissue. The explanation of tissue donation after cardiac death is often given by the attending physician, and it is not a little recognized that the attending physician is the same as the tissue transplant physician/surgeon. In this way, considering the unavoidable circumstances depending on the donor hospital, in this case it is desirable to have the signature of the witness (nurse, etc.). Furthermore, it is recommended that third-party doctors or tissue transplant coordinators other than tissue transplant physicians/surgeons obtain informed consent by requesting the participation of the Japan Organ Transplant Network coordinators. The explainer must sign by hand to clarify his/her identity, and hand-written signature of the consenter is necessary to clarify the intention of the donor family. The consent form for tissue donation shall be preserved at the donor hospital, and a copy thereof shall be preserved at the donor family, the preservation facility, and the tissues mediation agency, respectively. It will be preserved for 20 years at the donor hospital and the preservation facility.

Regarding the donation for the tissue transplantation (skin, blood vessel, bone/ligament, amniotic membrane, pancreatic islets, heart valve, etc.) that have been removed by surgery and are no longer medically needed, the name of the person himself/herself and the name of the explainer should be written by oneself, and the consent form for the tissue donation will be preserved at the donor hospital, and its copy will be preserved by the donor, and at the preservation facility and the tissues mediation agency.

1-3-2. Precautions regarding the contents of informed consent

It is necessary to specify the name of tissues donated in the tissue donation consent form, and for those that can be removed from a wide range of areas such as skin and blood vessels, it is important to specify the site and range in detail and obtain consent.

1-3-3. Clarification of matters related to research use and disposal of tissues, and handling when not in use

The primary purpose of providing human tissues is to use it for the transplantation, but if there is a problem in using it for the transplantation due to infection or other reasons, the tissue may be used for research purposes. That is, if the donated tissue is not suitable for the transplantation, it may be applied to the purpose of the research with the approval of the Ethics Committee, etc. in the presence of the informed consent. Alternatively, it is required to explain in advance that it may be discarded, and specify that fact in the tissue donation consent form.

2. ENSURING THE SAFETY OF TISSUE TRANSPLANTATION

On December 26, 2000, a notification from the Director General (Notification No. 1314) stating "Ensuring the Quality and Safety of Pharmaceutical Products Manufactured from Human/Animal-derived Materials" was issued by Pharmaceutical Safety Bureau of the former MHW (Reference 1). This is a notification from the Director of the Pharmaceutical Safety Bureau of the former MHW to the governors of each prefecture, and is a notification to manufacturers and companies that mainly handle pharmaceutical products manufactured from human/animal-derived materials. It should also be adhered to in the tissue bank and the allograft (homograft) bank that handle human tissues. JSTT considers that safety management must be carried out strictly in compliance with the principles presented in that notification even in the tissue "bank" system. In this notification text by the former Pharmaceutical Safety Bureau, "manufacturer" can be considered to correspond to the tissue bank that supplies human tissue to the transplant facility in terms of safety management, and "manufacturing process" to correspond to the human tissue preservation process. In addition, even if the recovery, storage, and use are carried out only within the facility, it is considered that the same guarantee is required for safety management. In the case of tissues subject to the "Act on Securing the Safety of Regenerative Medicine", "Regulation for Enforcement of Act on Securing Safety of Regenerative Medicine" and "Order for Enforcement of the Act on Securing Safety of Regenerative Medicine", it is required to comply with the Act, Regulation for Enforcement and Order for Enforcement.

When human tissue preserved by freezing, etc. is applied to clinical practice, it is extremely important to eliminate the risk of infectious microorganisms and substances. In order to avoid the danger from infectious microorganisms and substances, the

following multi-layered measures must be taken:

2-1. Confirmation of the presence or absence of infectious diseases (donor criteria).
2-2. Prevention of contamination in tissue processing and appropriate microbial clearance.
2-3. Implementation of tests and examination at each step of processing and usage.
2-4. Implementation of sterilization of tissues at each step by validated methods..
2-5. Preservation of these records for 20 years.

3. EXCLUSION CRITERIA FOR TISSUE DONORS

3-1 Medical Indication Criteria for Tissue Transplantation from the Deceased Donor (Table 1)

The medical indication criteria for the deceased donors in the tissue transplantation are shown below. Age limit is a rough guide. The time from cardiac arrest to the recovery takes into account the ischemic limits of each tissue. Common exclusion items are common to each tissue, and tissue-specific exclusion items are individual-specific exclusion items for each tissue. Interviews will be conducted at any time regarding overseas travel history and residence history. If new findings are obtained in the future, the criteria will be reviewed from time to time.

	islet	heart valve/vessel	skin	bone	cornea
age limmit	≦70y.o.	≦70y.o.	≦75y.o.	None	None
acceptable limit of warm ischemia	≦30min	≦12hr (≦6hr desirable)			≦24hr (≦12hr desirable)
common exclusion items	1. systemic infectious diseases (bacterial, viral, fungal) Local infectious diseases such as pneumonia are judged by the procurement team and by the test results after the removal. 2. syphilis-positive (Note 1), HBsAg/HCV Ab (Note 2)/HIV Ab/HTLV-1 Ab-positive 3. Creutzfeldt-Jakob disease (including vCJD) and its suspicious case 4. Malignant tumors (Note 1), hematopoietic tumors such as leukemia and malignant lymphoma If 5 years have passed since the treatment for primary brain tumor or solid cancer and the doctor in charge of tumor treatment judges that the tumor has been completely cured, the medical director of the tissue bank dispatching the procurement team will decide whether or not to retrieve the tissue based on that information. Regarding the appropriateness of transplantation, the transplant doctor shall decide with a sufficient explanation including risks based on the above information, and in the presence of the consent of the patient. 5. Autoimmune diseases such as collagen disease (Note 1, 3) 6. Death of unknown cause Note 1: Cornea can be donated in syphilis, extraocular malignant tumors and autoimmune diseases such as collagen disease. However, malignant lymphomas such as intraocular malignancies, leukemia, Hodgkin's disease, and non-Hodgkin's lymphoma are excluded. Note 2 The tissues can be donated if HCV-RNA is negative. Note 3: At this time, islets are only possible if other organs such as the kidneys are removed. In the case of autoimmune diseases, it is necessary to consider carefully whether or not to donate it.				
tissue-specific exclusion items	diabetes acute/chronic pancreatitis alcohol addiction functional/organic impairment of pancreas considered to be not suitable for transplantation	valvular diseases post-open heart surgery Marfan syndrome arteriosclerosis vascular diseases (above are not an absolute contraindication, and the suitability is carefully examined)	skin infectioun dermatitis damaged skin due to soft tissue trauma and compression necrosis including long-term bed rest drug addiction (taking toxic drugs, infiltrating toxic chemicals into the skin) burn or chemical burn	bone abnormalities due to serious metabolic/endocrine disorders bacterial/fungal focus and tissues near open wounds	subacute sclerosing panencephalitis, progressive multifocal leukoencephalopathy, etc.due to slow virus infection active viral encephalitis encephalitis of unknown cause progressive encephalopathy Reye's syndrome central nervous system disease of unknown cause intraocular malignancies

3-2 Exclusion Criteria for Tissue Donors

Human tissues should not be recovered or used if the donor falls under any of the below described specific diseases or conditions. In addition, it is necessary to conduct detailed inspections and palpations of donor's organs and tissues as much as possible, interview the donor's next-of-kin and also check the medical records.

The results of a pathological autopsy, if performed, must be reviewed. As for various inspection methods, the most appropriate method at that time should be adopted.

In addition, regarding items such as interviews and tests and their methods, the methods should be reviewed as needed in view of new knowledge about infectious diseases and advances in academics and technology. It is desirable that experts from related academic societies will cooperate and participate in the process of updating the criteria or collection and evaluation of the information of infectious disease related to the transplantation.

Based on the above-mentioned notification of Pharmaceutical Safety Bureau of the former MHW, the tissue recovery from those who fall under the following items is prohibited. In addition, diseases newly notified or communicated by the Ministry of Health, Labor and Welfare will be immediately considered, and the criteria for the transplantation will be changed in a timely manner.

3-2-1 Exclusion criteria for tissue donors in general

3-2-1-1 Death of unknown cause

3-2-1-2 Sepsis or other systemic infectious diseases

3-2-1-3 Creutzfeldt-Jakob disease (including vCJD) and its suspicion (Note 1.1, 1-2 and 1.3)

3-2-1-4 Malignant tumors (including hematopoietic neoplasms such as leukemia and malignant lymphoma)

Basal cell carcinoma of the skin and primary brain tumors other than those undergoing multiple craniotomy are excluded from the exclusion items. If it is judged that the tumor has been completely cured by the treatment, it does not fall under the exclusion item. Whether or not it is completely cured is left to the judgment of the doctor in charge of tumor treatment, and based on that

information, the medical director of the tissue bank decides whether or not to retrieve the tissues. The final decision on the transplantation will be fully explained based on the above information, including risks, and will be decided by the recipient doctor with the consent of the patient.

3-2-1-5 Severe metabolic or endocrine diseases, hematological diseases and auto-immune disorders such as or collagen disease

3-2-1-6 Syphilis (Note 2)

If it is judged that the patient has been completely cured by the treatment, it does not fall under the exclusion items.

3-2-1-7 Hepatitis B virus (HBV) infection (HBsAg positive)

3-2-1-8 Hepatitis C virus (HCV) infection (HCV Ab or HCV・RNA positive) (Note 3)

If it is judged that the patient has been completely cured by the treatment (HCV-RNA negative, SVR), it does not fall under the exclusion items.

3-2-1-9 Human immunodeficiency virus (HIV) infection

If the result of the screening test is indeterminant or positive for HIV antibody, the confirmation test is performed by HIV-1/2 antibody confirmation test and HIV-1 nucleic acid amplification test (NAT).

3-2-1-10 Adult T-cell Leukemia (ATL)

When the result of the screening test is indeterminant or positive for HTLV-1 antibody, the confirmation test is performed by line immunoassay (LIA). If LIA is positive, it is judged finally as positive for HTLV-1 antibody. If the judgment is indeterminant by the LIA, the HTLV-1 provirus is detected by the HTLV-1 NAT (PCR).

3-2-1-11 Parvovirus B19 infection (Note 4)

3-2-1-12 West Nile Virus infection (West Nile fever) (see Note 5)

3-2-1-13 Severe Acute Respiratory Syndrome（SARS-CoV）and COVID-19 (SARS-CoV-2) (Note 6.1 and 6.2)

3-2-1-14 Rabies (Note 7)

3-2-1-15 Amoeba encephalitis due to *balamuthia mandrillaris* (Granulomatous Amebic Encephalitis) (Note 8)

3-2-1-16 Zika virus disease (Note 9)

3-2-1-17 Others who meet the exclusion criteria specific to each tissue.

3-2-1-18 Those who died due to abuse or those who died on suspicion of abuse. (Note 10)

3-2-1-19 Those with intellectual disabilities that make it difficult to effectively express their intentions regarding organ donation.

From August 1, 2022, when under 15 years old, it is possible to donate organs

and/or tissues regardless of presence of intellectual disability with the written consent of the family.

All these infections and diseases listed above should be denied by interview and tests (serological test, nucleic acid amplification test, etc.). In addition, cytomegalovirus infection and Epstein-Barr virus infection should be denied by inspection as necessary.

Note 1.1

1. Prion disease is a disease in which a normal prion protein (PrP^{C}) changes to a transmissible abnormal prion protein (PrP^{Sc}) for some reason and accumulates in the central nervous system, causing rapid degeneration of nerve cells. It is roughly divided into three types: idiopathic (sporadic, sCJD), hereditary (familial (gCJD)), and acquired (Kuru disease, iatrogenic, mutant type (vCJD)). Normal PrP^{C} is degraded by proteolytic enzymes, but abnormal PrP^{Sc} is not digested by proteolytic enzymes, is insoluble, easily aggregates, and accumulates in the brain. In acquired prion disease, exogenous PrP^{Sc} comes into contact with normal PrP^{C}, causing a chain reaction in which PrP^{C} is converted to PrP^{Sc}, and the converted PrP^{Sc} accumulates in the brain to cause the disease.
2. A definitive diagnosis is made if CJD-specific pathological findings are found in the brain tissue, or if PrP^{Sc} is detected by Western blotting or immunohistological examination. Progressive dementia, periodic synchronous discharge (PSD) on the electroencephalogram, and 14-3-3 protein positive in the cerebrospinal fluid also strongly suggest CJD. In the vCJD case, no EEG PSD was observed, and MRI showed a high signal of thalamic pulvinar as a specific finding. Brain CT shows atrophy of the cerebral cortex, ventricular enlargement, and diffuse low density of the white matter, and in severe cases, it has a spongy appearance. Detection of PrP^{Sc} by palatine tonsil biopsy or detection of PrP^{Sc} by RT-QuIC (Real-time quaking induced conversion) method in cerebrospinal fluid and other tissues is also useful.

Note 1.2

As of June 2001, to rule out the potential for transmission of variant Creutzfeld-Jakob disease (vCJD), each tissue bank should thoroughly consider and judge regarding tissue recovery from donors with the following history until new facts are discovered or regulatory changes are made:

1. Dementia or other central nervous system manifestation of unknown causes, which are the symptom of CJD
2. Family history of CJD and related illnesses

3. History of injections of human-derived growth hormone
4. History of corneal transplantation
5. History of brain surgery with a dura mater implant
6. History of human placenta extract (placenta) injection

【Reference 1】Since the possibility of transmission of vCJD via human placenta extract (placenta) injection cannot be ruled out, the director of the Health Bureau of the Ministry of Health, Labor and Welfare asked the director of Japan Organ Transplant Network and each Eye Bank to strengthen the interview regarding the history of human placenta extract injection, and the following notice was issued (Notification No.0927004, September 27, 2006).

"In principle, donation of organs from persons who have used human placenta extract (placenta) injection will be postponed, but in view of the urgency and substitutability of the transplantation medicine, for the time being, in case that the recipient candidate will receive appropriate explanations from the transplant doctor about vCJD, its infection risk associated with the transplantation, and points of attention after the transplantation, and in addition if his/her intention to receive the donation of the organ from the organ donor is made clear, this does not apply. When a transplant is performed by this handling, the organ transplant network should encourage the transplant doctor to sufficiently follow up the recipient regarding the onset of vCJD".

【Reference 2】
1. The human placenta extract (placenta) injection is manufactured from the placenta of a woman who has never traveled abroad, has no viral infections such as HBV, HCV, and HIV, and has a normal delivery in Japan.
2. To date, there have been no reports showing that vCJD was transmitted by the use of blood products and placental extract injections, and the FDA and EMEA do not regulate blood donation.
3. The outbreak of iatrogenic prion disease in Japan is due to human dural transplantation (154 cases) except for one case of variant CJD (vCJD).
4. In the "Prion Disease Infection Prevention Guideline 2020" of the Japanese Society of Neurology, and the "Prion Disease Treatment Guideline 2023 (provisional version)" of the Research Group on Prion Disease and Slow Virus Infection (Health Labor Sciences Research Grant, Provisional Edition), human placenta extract injection is not considered a risk factor for prion disease infection.

Note 1.3

It is necessary to strive to understand overseas travel history. As a precautionary measure for the time being, each tissue bank should thoroughly consider and judge the recovery of tissues from those who have stayed in the following European countries. (January 27, 2010, Notification No.0127 No. 2)

1. Those who have stayed (resident) in the UK for a total of 1 month (31 days) or more from 1980 to 1996.
2. Those who have stayed (resident) in the UK for a total of 6 months or more from 1997 to 2004.
3. Those who have stayed (resident) in Ireland, Italy, the Netherlands, Saudi Arabia, Spain, Germany, France, Belgium and Portugal for a total of 6 months or more from 1980 to 2004.
4. Those who have stayed (resident) in Switzerland for a total of 6 months or more from 1980 to today.
5. Those who have stayed (resident) in Austria, Greece, Sweden, Denmark, Finland and Luxembourg from 1980 to 2004 for a total of 5 years or more.
6. Those who have stayed (resident) in Iceland, Albania, Andrra, Croatia, San Marino, Slovakia, Slovenia, Serbia, (Kosovo), Czech Republic, Norway, Vatican, Hungary, Bulgaria, Poland, Bosnia and Herzegovina, Macedonia, Malta, Monaco, Montenegro, Lichtenstein, Romania for a total of 5 years or more from 1980 to today.

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. When the STS method is negative with the antibody titer less than 1 x, it is necessary to switch to a more sensitive test.
2. TP antigen method (specific antigen reaction) – the TPHA method is considered negative at less than 80 x, and the FTA-ABS method (quantitative) is considered negative at less than 20 x.

Note 3

1. Even if the HCV antibody is positive, in case that its titer is low, it is highly probable that HCV･RNA is negative. Therefore, when antibody titer is low, it is desirable to confirm it by detecting HCV･RNA. Even if the HCV antibody is positive with a low titer,

the tissue can be donated as long as HCV･RNA is negative.
2. HCV antibody low titer positive is defined as 2^4 or less by the PA method, 2^5 or less by the PHA method, less than 15 by the AxSYM method, and less than 5 by the Lumipulse method.

Note 4

According to the notification of the Pharmaceutical and Medical Safety Bureau of the former MHW, Parvovirus B19 must be equally measured in accordance with hepatitis virus B and C 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.

1. Human parvovirus B19 (PVB19) is a single-stranded DNA virus belonging to the genus Parvoviridae, subfamily Erythrovirus, and infects only humans.
2. PVB19 infects erythrocyte progenitor cells via P antigen (globoside) of the erythrocyte-type antigen and induces apoptosis. P-antigen is also distributed in megakaryocytes, endothelial cells, placenta, fetal liver and fetal myocardium, etc.
3. It is transmitted by droplet infection (trans-airway infection) and contact infection, and one week after infection, it causes viremia (incubation period is 4 to 15 days) and presents with flu-like symptoms. One week before the onset of symptoms is the time of virus excretion and is highly infectious. It then presents with a characteristic rash, at which point viremia has disappeared and is almost non-infectious.
4. A typical symptom is butterfly erythema, which is common in children, and the name "apple disease" is derived from this (infectious erythema). Adults present with a variety of symptoms, and differential diagnosis may be difficult. Most have a benign course, but care should be taken when hemolytic anemia is the underlying disorder, as it may cause chronic anemia and aplastic crisis. Patients with immunodeficiency, patients undergoing chemotherapy for blood disorders, and organ transplant patients may develop persistent infections, which may become severe. About 1/4 of the infected cases are subclinical infections, but it is said that there are also infections from subclinical infected persons.
5. Infection from blood transfusions, fresh frozen plasma and fractionated plasma products has become a problem. Although PVB19 is not subject to testing under the Biological Raw Materials Standards based on the Pharmaceutical Affairs Law, according to the notification of the Pharmaceutical and Medical Safety Bureau of the former MHW, parvovirus B19 infections should be denied by interviews and tests (serological tests and

nucleic acid tests) as well as HBV, HCV, HIV and HTLV-1. Since 1997, screening tests using the agglutination method (PHA method) have been introduced for plasma fractionated products. Since 2008, the CLEIA method (chemiluminescent enzyme immunoassay), which has higher detection sensitivity, has been adopted, and the incidence of infection has decreased, but the current situation is that it has not been completely prevented. In particular, blood transfusions from blood donors in the early stages of infection have become a problem.

6. IgM antibody is detected about 2 weeks after the initial infection and lasts for about 3 months, and IgG antibody is detected several days after the positive conversion of IgM antibody and lasts for a lifetime. PVB19 DNA peaks 1 week after infection, decreases sharply 2-3 weeks, and then gradually decays after 6 months or more. The PVB19 antigen becomes positive 1 week after infection and becomes negative 2-3 weeks after infection.

7. For IgM antibody-positive cases, PVB19 antigen-positive cases, and PVB19 DNA-positive cases, each tissue bank should be thoroughly examined and judged.

Note 5

Centers for Disease Control and Prevention (CDC) reported in its official report that West Nile Virus is transmitted via blood transfusion and organ transplant. In accordance with this report, for the time being after November 2002, a temporary safety measure has been taken, namely prior to donation, a thorough interview is required, when the donor has a travel history within 4 weeks prior to donation to the areas affected by West Nile Virus, including the US. In addition, it is required to confirm that the PCR test is not positive for West Nile virus and the West Nile virus IgM test is not positive in the donor, and if it is positive, it is not used for the transplantation (October 25, 2006, Issue No. 1025003).

Note 6.1

1. Regarding donors of organs or hematopoietic stem cells (hereinafter referred to as "organs, etc."), it is required to confirm their overseas travel history and stay history within 3 weeks before donation, and not to use the candidate's organs, etc. for transplantation, if he/she has a history of overseas travel or stay in areas where SARS "Recent Intraregional Propagation" announced by WHO is suspected.

2. Regarding candidates for donation of organs, etc., it is required to strengthen the interview as to whether or not they fall under the “possible cases” in Attachment 1 "Case definitions for reporting suspected and possible cases of SARS" (hereinafter referred to

as "case definitions") of “Revision of case definition and accompanying administrative examination of SARS coronavirus” (May 8, 2003, Notification No. 0508001). If the case falls under the “possible case”, the candidate's organs, etc. should not be used for transplantation for 3 months after the treatment is completed and the patient has completely recovered.

3. Regarding candidates for donation of organs, etc., it is required to strengthen the interview as to whether they fall under the "suspicious case" in the "case definition", and if so, the candidate's organs, etc. should not be used for transplantation for one month after the treatment is completed and the patient has completely recovered.

4. Regarding candidates for donation of organs, etc., those who have nursed or cared for those who fall under the "possible cases" (above 2) or "suspected cases" (above 3), those who lived together, or those who was in direct contact with airway secretions or body fluids within 3 weeks before donation, should not donate tissues or organs.

Note 6.2

1. The new coronavirus is the seventh coronavirus that infects humans, in addition to the four seasonal coronaviruses, SARS coronavirus (SARS-CoV) and MERS coronavirus (MERS-CoV), and named SARS-CoV-2. SARS-CoV-2 infection causes pneumonia, intravascular coagulation syndrome, thrombosis/embolism, etc., and when it becomes severe, it leads to respiratory failure and multiple organ failure. The above pathological condition caused by SARS-CoV-2 infection was named COVID-19, and after the first case was reported in Wuhan, Hebei Province, China in January 2020, it spread all over the world and in March 2020 WHO issued a pandemic declaration.

2. Office for Transplant Medicine, the Ministry of Health, Labor and Welfare's has issued a notification to each academic society related to transplant medicine and the Japan Organ Transplant Network that "PCR tests should be performed on donor candidates and if the result is positive, do not perform organ donation from the said candidate." (Notification No. 0421, April 21, 2020). Then in July 2021, Office for Transplant Medicine provided information that “In the United States, a lung transplant was performed from a donor whose nasopharyngeal specimen was negative for PCR, and the surgeon and recipient were infected with SARS-CoV-2”, and “Later a PCR test was performed on a specimen derived from the lower respiratory tract of the transplanted lung, and it was found to be positive”. Based on this information, a notification was made stating that "When donating organs, PCR tests should be performed on lower respiratory tract secretions as much as possible." (Notification No. 0721, July 21, 2021).

3. If the tissue is donated together with the organ donation, it will be donated after

confirming the negative by the PCR test, but even if the tissue is donated alone, the negative should also be confirmed by the PCR test. Although the window period of SARS-CoV-2 is short, in order to avoid slipping through the window period, it is necessary to inquire about the behavior history of the last two weeks, and to confirm especially whether there is close contact with infected people and behavior history with high risk of infection.

4. It is unclear at this time whether the infectivity of SARS-CoV-2 is diminished in the process of processing and storage of the provided tissue. In the process of tissue procurement, processing and preservation, it is important to pay close attention to infection, strive to prevent infection, and pay attention to ensuring the safety.

Note 7

1. Rabies virus is known to be transmitted by organ transplantation, so if the cause of death is suspected to be this disease, his/her tissue should not be donated.

2. It is necessary to check the overseas travel history of the tissue donor within the past 7 years and the history of injury such as bites by mammals overseas, and if there is an overseas travel history and injury history, the transplant physician/surgeon must fully explain to the transplant patient concerning the rabies and infection risk associated with the transplantation.

3. If a transplantation is performed in case above 2, transplant physician/surgeon should follow up the transplant patient with respect to the development of rabies (June 29, 2005, Notification No. 0629002).

Note 8

1. CDC reports that after the organ transplantation conducted in the United States in 2009 and 2010, four patients developed amoebic encephalitis due to *balamuthia mandrillaris* infection, which is thought to be of donor origin, and three of them died.

2. In response to this, there was an administrative communication from the Director of the Office for transplant medicine, Disease Control Division, Health Service Bureau, MHLW (December 2, 2010 Office Memorandum), which states that the National Institute of Infectious Diseases examined and provided information to call attention in the "Infectious Disease Health Risk Information Evaluation Study Group and Biological Product-derived Infectious Disease Information Collection Review Committee" (45th).

3. *Balamuthia mandrillaris* is found in water, soil and dust around the world and infect not only immunocompromised hosts but also normal hosts. The onset is insidious, with the appearance of ulcerative skin lesions, followed by nervous system symptoms

(changes in mental status, seizures, headache, etc.).

4. Contrast-enhanced CT and contrast-enhanced MRI show multiple nodular lesions, typically ring-shaped. Bleeding in the lesion is an important diagnostic clue. In the cerebrospinal fluid, the white blood cell count increases (mainly lymphocytes), sugar is normal or low, and protein is often significantly increased.

5. *Balamuthia mandrillaris* can be identified in biopsy specimens of brain or skin lesions by microscopic examination, PCR and immunohistochemistry, but *Balamuthia mandrillaris* is rarely identified in the cerebrospinal fluid.

6. If the cause of death of the donor is amoebic encephalitis, especially if clinically suspected to be infected with *balamuthia mandrillaris*, or if subsequent examinations reveal granulomatous amoebic encephalitis due to *balamuthia mandrillaris*, careful action is required including discontinuation of the tissue transplantation. For that purpose, it is necessary to establish a communication system that guarantees prompt and close information sharing between the donor hospital, the organ/tissue transplant facility, the Japan Organ Transplant Network, the Japan Society for Transplantation, the JSTT, and the tissue bank.

Note 9

1. Zika virus disease is an infectious disease caused by Zika virus infection, and is a mosquito-borne infectious disease caused by being bitten by mosquitoes (Aedes aegypti, Aedes albopictus) carrying Zika virus.

2. Other transmission routes include mother-to-child transmission (intrauterine infection), blood transfusion, and sexual activity. Cases of sexually transmitted infections from men returning from endemic areas to partners who have not traveled (including infections from men to men), and infections from women returning from endemic areas to partners who have not traveled have been reported. Zika virus RNA has been detected in male semen and urine in those who developed Zika virus disease. In addition, Zika virus RNA has been detected in the cervical mucus of affected women.

3. The incubation period is 2 to 12 days (mostly 2 to 7 days), and symptoms include mild fever (38.5°C or below), headache, arthralgia, muscle pain, maculopapular rash, conjunctivitis, fatigue, malaise, and thrombocytopenia. Zika virus has neurotropism, and complications such as Guillain-Barré syndrome, acute myelitis, and meningoencephalitis have been reported, and viral RNA has been detected in cerebrospinal fluid. It is generally milder than other mosquito-borne infections and follows a benign course.

4. Zika virus disease develops in about 20% of infected people, and 80% are asymptomatic

infections.

5. Infected pregnant women may develop microcephaly due to mother-to-child transmission. Zika virus RNA has been detected in amniotic fluid, blood of dead fetuses, and brain tissue of pregnant women with confirmed fetal microcephaly. Infection during early pregnancy is said to have a strong correlation with the risk of developing hydrocephalus, but the risk of developing infection during the second and third trimesters cannot be denied.

6. Regarding the duration of Zika virus infection, sexually transmitted cases indicate that Zika virus infectivity may be maintained for about 41 days after the onset of Zika virus disease. There is a report that Zika virus RNA was detected by PCR up to 58 days after onset (the duration of viremia was about 50 days) in blood and 93 days after onset (however, Zika virus infectivity was limited to 41 days after onset) in semen. Cervical mucus, nerve tissue, cerebrospinal fluid, etc. have not been clarified at this time. There are reports that viral RNA was detected in breast milk 8 days after childbirth, but the virus has not been isolated, and no cases of infection via saliva, urine, or breast milk have been reported at this time.

7. WHO, US CDC, ECDC (European CDC) and Japanese provisional guidance state:

① Refrain from donating blood within 4 weeks from the date of return from the endemic area

② Those returning from the endemic area are recommended to use condoms or refrain from sexual activity for at least 6 months regardless of infection.

③ Women returning from endemic areas should postpone their pregnancy plans for at least 6 months.

4. Based on the questionnaire on organ donation prepared by the Transplantation Medical Measures Promotion Office of the MHLW, a thorough interview is recommended as to whether or not he/she has a history of staying (resident) within the previous 4 weeks, in Brazil, Colombia, French Giana, Panama, Haitian, El Salvador, Guatemala, Mexico, Suriname, Honduras, Martinique, Paraguay, Puerto Rico, and Venezuela. If any of the above items apply, and especially if he/she has clinical symptoms such as fever below 38.5 ° C, headache, arthralgia, myalgia, maculopapular rash, fatigue and malaise, it is said that information on them should be provided to the transplant facility.

Note 10

If the donor is under the age of 18, medical examination findings and other circumstances must confirm that the child is not an abused child. If there is any suspicion of abuse, it is necessary to notify the local child consultation center based on the Child

Abuse Prevention Act. In this case, neither tissue nor organ can be donated. If there is no suspicion of abuse and a notification based on the Child Abuse Prevention Act is not made, it is possible to donate organs and tissues. The transplant coordinator should confirm and record that the donor hospital has determined that there is no abuse in the case.

Regarding the interviews on each of the above items, the Japan Organ Transplant Network has prepared a "Questionnaire regarding Organ Donation", and when organ donation is performed at the same time, the contents of this questionnaire will be checked. It is desirable to apply this questionnaire also when providing the tissue only. This questionnaire also covers Creutzfeldt-Jakob disease, West Nile fever/encephalitis, rabies, and Zika virus, as well as whether it is possible to effectively express intentions regarding organ donation. For items other than these, a further detailed medical interview is necessary. It is noted that this does not apply when it can be confirmed by clinical diagnosis or examination.

4. PROCESSING AND STORAGE OF HUMAN TISSUES

4-1. Processing and Storage of Human Tissues

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 pay close attention to prevent contamination and perform appropriate microbiological tests. The safety in the process of procured human tissues and its efficacy for the transplantation must be confirmed.

4-1-1. It is required that the safety has been sufficiently confirmed in all equipment, instruments, chemicals, and air and water environments used for processing and preserving human tissue.

4-1-2. In the workplace where the procured human tissue is processed, it is required that work is done in sterile environmental equipment using sterilized instrument to prevent contamination of human tissue. Attention should also be paid to the prevention of transmission of infectious diseases through human tissues to those engaged in the work by wearing preventive clothing.

4-1-3. Using a part of the recovered tissue, culture tests for bacteria and fungi, etc. must be done.

4-1-4. In the process of treating the recovered human tissues, an appropriate microbial treatment such as sterilization and disinfection, and an appropriate culture test or test

for bacteria, fungi, etc. at each step of the processing procedure must be done.
4-1-5. Regarding the work environment for processing and preserving the recovered human tissues, care should be taken to maintain a constant cleanliness, and create a work environment that is safe for workers. In addition, checking of quality of the work environment on a regular basis is required.
4-1-6. For the recovered human tissues, a certain storage period must be set until the culture results of bacteria, fungi, acid-fast bacilli, etc. for each tissue, and the recovered tissue should not be used for the transplantation unless time has passed and test results have been obtained. However, this does not apply to fresh use of cornea, skin, pancreatic islet, amniotic membrane, etc.
4-1-7. It is necessary to create and save the above record. The tissue bank should prepare a Standard Operating Procedure manual for processing and storing the recovered tissue. In addition, a record of the processing and storage status of the recovered tissue must be created. An internal evaluation of the content on a regular basis along with striving for quality control, and an evaluation by an external organization as necessary are required.
4-1-8. If any problems with human tissue transplantation occurs, it is necessary to contact the JSTT immediately. Furthermore, it is desirable to contact Office for Transplant Medicine of the MHLW, and cooperate in strengthening infection crisis management (May 20, 2002, Office for Transplant Medicine, Disease Control Division, Health Service Bureau, MHLW, Director Notification No. 0520002) .

4-2. Prevention of Contamination in Processing and Storage

Specific items to be observed regarding contamination prevention and appropriate microbial clearance in the process of processing and preserving human tissues removed from those that meet the donor criteria are shown below.

4-2-1. Bacterial (including tubercle bacilli) and fungal culture tests are necessary by using a part of the procured tissue, etc. as a material. This includes Gram-positive/negative bacteria, aerobic/anaerobic bacteria, tubercle bacilli (acid-fast bacteria), chlamydia, and mycoplasma.
4-2-2. In the tissue preservation process, it is required to operate aseptically in a clean bench.
4-2-3. After the sterilization operation with the combined antibacterial agent, the bacterial and fungal culture tests are recommended to repeat, and then the cryopreservation procedure is started. Conventionally, 10% calf serum has been used,

but it should not be used for the time being because the association with BSE (bovine spongiform encephalopathy) cannot be ruled out. It has been reported that there is no change in the quality of cryopreserved tissue without its use.
4-2-4. When using the tissue, it is desirable to perform a bacterial/fungal culture test by using the preservation solution, the remaining part of the tissue to be used after thawing, or a swab on the surface of the tissue to be used.
4-2-5. The above methods and results must be recorded in an appropriate form and preserved for 20 years.

Note 1
In case a weak positive reaction to resident microbe is observed at tests of [4-2-1], and then found negative with tests mentioned in [4-2-3], judgement of tissue eligibility must be made after thorough checking.

Note 2
Where results of tests mentioned in [4-2-3]turned bacteria/fungi positive, the tissue must not be applied to clinical purpose and may be used for research purposes based upon the consent obtained from the donor party.

Note 3
These items do not apply to fresh use of cornea, skin, pancreatic islets, amniotic membrane, etc.

4-3. Human Tissue Distribution for Clinical Application to a Transplant Facility

4-3-1. When a tissue bank distributes human tissues to a transplant facility, the distribution must be conducted fairly in accordance with an explicitly written standards. At that time, care should be taken to maintain the fairness of transplantation opportunities in the selection of recipients.
4-3-2. When the tissue bank supplies human tissue to the transplant facility, it should also provide information on the items of the donor screening test performed, the test method, the result, the processing method, etc.
4-3-3. The tissue bank preserves and manages records related to the supply of human tissues to transplant facilities while paying attention to the protection of privacy, and the system that enables to confirm the records of donors, processing/preservation processes, and recipients of the tissue transplants as necessary should be established. In

addition, each record shall be retained for a minimum of 20 years, but it shall be retained as much as possible after the expiration of that period.

4-3-4. Before using human tissue for transplantation at a transplantation facility, the written consent of the recipient must be obtained. Additionally, in order to obtain consent, the doctor in charge of the facility must fully explain the safety including the potential risk and the effectiveness of tissue transplantation to the recipient side.

4-3-5. When human tissue is used for transplantation at a transplant facility, the tissue provided, the bank name, the identification number of human tissue provided by the bank, etc. should be recorded in the medical record. And an information manager should be assigned to as needed, and a system that enables retrospective surveys and follow-up surveys to be conducted under the information manager should be established.

4-3-6. Tissue banks and transplant facilities strictly manage information that identifies the recipient side or information that the recipient side does not want to be disclosed, and that information must not be leaked. For this purpose, it is necessary to appoint an information manager as described in the chapter [3-6] and [5-6] of "GUIDELINE ON ETHICAL ISSUES IN APPLICATION OF HUMAN TISSUE TO MEDICAL PRACTICE". The representative of the tissue bank is in charge of the information manager.

4-3-7. As a non-profit/public institution, the tissue bank must not receive, request or promise profits from transplant facilities, patients, etc. for the purpose of profit as compensation other than necessary expenses. However, administrative expenses (transportation, communication, coordination and personnel expenses) and bank expenses (costs related to procurement, examination, preservation or transfer of human tissue) that are normally required for activities of the tissue bank are not regarded as commercial consideration.

Reference

"Regulation of the safety and quality in medical products manufactured from human/animal-derived material"
(No. 1314, The Pharmaceutical Safety Bureau of the former MHW)
December 26, 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. Therefore, from this point of view, it is necessary to take consistent measures from cell / tissue collection to manufacturing and use.

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 Guideline on the Safety, Storage, and Application of Human Tissue in Medical Practice Page14 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 tuberculosa 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.