Guideline on Ensuring Quality and Safety of Products Derived from Processed Human Cells and Tissues (allogeneic cells)

Introduction

1. The guideline defines basic technical requirements to ensure quality and safety of drugs or medical devices derived from processed allogeneic human cells and tissues (excluding autologous cells and tissues) (hereinafter referred to as "cell and tissue processed products, etc.").

   The cell and tissue processed products, etc. widely vary in terms of the type, characteristics, and clinical application, and this field is advancing day by day with scientific progress and accumulation of experience. Uniform application of the guideline or assumption that the guideline covers all requirements may not be always appropriate. Studies and evaluation of individual drugs, etc. should be performed flexibly on a case-by-case basis according to reasonable grounds reflecting the current academic progress in view of the objective of the guideline.

2. An objective of inspection for compliance with the guideline at the time of application for confirmation according to PMSB Notification No. 906, dated July 30, 1999, of the Pharmaceutical and Medical Safety Bureau, Ministry of Health and Welfare (MHW) "Ensuring Quality and Safety of Medical Devices or Drugs Using Cell and Tissue" is to check whether there is any quality or safety problem that may preclude start of a clinical trial of the cell and tissue processed products, etc. For application for confirmation, therefore, data to be attached are not always required to meet all requirements and contents specified in the guideline. On the premise that data for ensuring the quality and safety at the time of application for marketing approval will be enriched and improved in accordance with the guideline as the clinical trial progresses, application for confirmation should be accompanied by submission of appropriate data that meet requirements for the objective and have been prepared rationally.

   In addition, the extent and degree of data required for confirmation vary depending on the origin of the product, target disease, target patient, application site, application method, processing method, etc., and the guideline may not indicate specific matters. Consultation with the Pharmaceuticals and Medical Devices Agency (PMDA) may be sought individually.

Contents

Chapter 1 General Provisions 4
Section 1 Objective 4
Section 2 Definitions 4
Chapter 2 Manufacturing method 4
Section 1 Source materials and production-related materials 4
1 Intended cells or tissues 4
(1) Origin and history and reason for selection 4
(2) Characteristics and qualification of cells or tissues eligible for source materials 4
(3) Donor records 5
(4) Collection, storage, and transportation of cells or tissues 5
2 Source materials and production-related materials other than intended cells or tissues 6
(1) Cell culture 6
(2) Combination with non-cellular or non-tissue ingredients 7
(3) If cells are genetically engineered (modified), ... 8
Section 2 Manufacturing process 9
1 Presence or absence of lot configuration and specification of lot 9
2 Manufacturing method 9
(1) Acceptance inspection 9
(2) Inactivation and removal of bacteria, fungi, viruses, etc. 9
(3) Mincing of tissue, separation of cells, isolation of specific cells, etc. 9
(4) Culture process 9
(5) Establishment and use of cell lines 9
(6) Cell banking 10
(7) Measures to prevent mix-up and cross contamination during the manufacturing process 10
3 Characterization of processed cells 10
4 Form and package of final product 10
5 Consistency of manufacturing method 10
6 Change of manufacturing method 10
Section 3 Quality control of final product 10
1 General introduction 10
2 Quality control method of final product 11
(1) Cell count and viability 11
(2) Identification 11
(3) Cell purity 11
(4) Studies for unintended biological active substances derived from cells 11
(5) Process-related impurities 12
(6) Sterility test and mycoplasma test 12

(7) Bacterial endotoxins 12
(8) Tests of viruses, etc. 12
(9) Primary performance 13
(10) Potency assay 13
(11) Mechanical suitability test 13
Chapter 3 Stability of cell and tissue processed products, etc. 13
Chapter 4 Nonclinical safety studies of cell and tissue processed products, etc. 13
Chapter 5 Primary efficacy or performance studies of cell and tissue processed products, etc. 14
Chapter 6 Biological disposition of cell and tissue processed products, etc. 15
Chapter 7 Clinical studies 15

Chapter 1 General Provisions

Section 1 Objective

The guideline defines basic technical requirements to ensure quality and safety of drugs or medical devices derived from processed allogeneic human cells and tissues (excluding autologous ones) (hereinafter referred to as "cell and tissue processed products, etc.").

Section 2 Definitions

The terms in the guideline are defined as follows:

1 The term "Processing of cells and tissues" refers to manipulations for the purpose of disease treatment or tissue repair or reconstruction, including artificial proliferation of cells and tissues, establishment of cell lines, treatment of cells and tissues with drugs for activation, modification of biological properties, combination with non-cellular or non-tissue ingredients, and genetic engineering (modifications).

The following manipulations are not deemed as processing: separation of tissue, mincing of tissue, separation of cells, isolation of specific cells, treatment with antibiotics, washing, sterilization by gamma rays, freezing, and thawing.

2 The term "Manufacturing" refers to activities including, in addition to processing, operations that do not alter the original properties of the cells or tissues such as separation of tissue, mincing of tissue, separation of cells, isolation of specific cells, treatment with antibiotics, washing, sterilization by gamma rays, freezing, and thawing, which are performed before release of the final product, a product using cells or tissues.

3 The term "Phenotype" refers to morphological and physiological properties expressed by a gene under certain environmental conditions.

4 The term "HLA typing" refers to activities for identification of the type of HLA (human leukocyte antigen), which is a major histocompatibility antigen in humans.

5 The term "Donor" refers to a person who provides cells or tissues as raw materials for cell and tissue processed products, etc.

6 The term "Gene transfer component" refers to a construct composed of a vector for transfer of the target gene into the target cells, the target gene, and pieces of base sequences encoding factors necessary for expression of its function.

Chapter 2 Manufacturing method

Section 1 Source materials and production-related materials

1 Intended cells or tissues

(1) Origin and history and reason for selection

The origin and history of cells or tissues used as a source material should be explained, and the reason for selection of the concerned cells or tissues should be clearly described.

(2) Characteristics and qualification of cells or tissues eligible for source materials

[1] Characteristics of biological structure and function and reason for selection

For the cells or tissues used as a source material, characteristics of the biological structure and functions should be described in terms of appropriately selected items, such as morphological characteristics, growth characteristics, biochemical markers, immunological markers, characteristic produced substances, HLA typing, and other

appropriate markers of genotype or phenotype. The reason for selecting the cells or tissues as raw material should be explained.

[2] Donor inclusion criteria, eligibility

Verification should be presented that the donor has been selected in an ethically appropriate manner. Inclusion criteria and eligibility criteria should be defined in consideration of age, gender, ethnic characteristics, medical history, health status, test items for various infections that may be transmitted via collected cells or tissues, immunocompatibility, etc. and justified.

Particularly, hepatitis B virus (HBV), hepatitis C virus (HCV), human immunodeficiency virus (HIV), human T-cell leukemia virus (HTLV), and parvovirus B19 infections should be ruled out based on medical interview and tests (serological test, nucleic acid amplification method, etc.). Cytomegalovirus, EB virus, and West Nile virus infections should be ruled out by tests as necessary.

In addition, medical conditions listed below should be inspected through medical history and interview. Based on the obtained information and presence or absence of prior blood transfusion and transplantation therapy, whether the individual is eligible for donation should be determined.

- Infections with bacteria such as *Treponema pallidum*, *Chlamydia*, *Neisseria gonorrhoeae*, and *Mycobacterium tuberculosis*
- Sepsis and suspected sepsis
- Malignancy
- Serious metabolic and endocrine disorders
- Collagen disease and blood disorders
- Liver disease
- Transmissible spongiform encephalopathy and suspected transmissible spongiform encephalopathy as well as other dementia

(3) Donor records

For cells or tissues used as a source material, donor records should be organized and retained to ensure that information necessary for ensuring safety is accessible. The measures should be presented in detail.

(4) Collection, storage, and transportation of cells or tissues

[1] Qualification of responsible person and collecting medical institutions

Technical requirements for responsible person and collecting medical institutions should be specified.

[2] Appropriateness of collection sites and collection method

Criteria for selecting cell collection sites and the collection method should be described. The selected sites and the method should be justified scientifically and ethically. For the collection method, apparatuses to be used and preventive measures against microbial contamination, mix-up, and cross-contamination should be described specifically.

[3] Provision of written information to and the obtainment of written informed consent from donor

Details of the provision of written information to and the obtainment of written informed consent from a donor before collection of cells or tissues should be specified.

[4] Protection of donor's personal information

Measures to protect the donor's personal information should be specified in detail.

[5] Tests and examinations to ensure the safety of donors

If tests or examinations to check the condition at the collection site are required to ensure safety of the donor during collection of cells or tissues, the details should be specified. In addition, actions to be taken in response to a problem with examination results, if any, should be specified in detail as well.

[6] Storage method and measures to prevent mix-up

If collected cells or tissues need to be stored for a certain period of time, the storage condition and period should be specified and justified. In addition, means, procedures, etc. to avoid mix-up should be explained in detail.

[7] Transportation method

If collected cells or tissues need to be transported, containers and procedures for transportation (including temperature control) should be specified and justified.

[8] Documentation and archiving method

Activities implemented according to [1] to [7] should be documented, and an appropriate method to archive the records should be specified.

2 Source materials and production-related materials other than intended cells or tissues

Source materials and production-related materials other than the intended cells or tissues should be specified, and their qualifications should be presented. Specifications should be established to implement appropriate quality control, as necessary.

If a biological product or a specified biological product is used as a source material, the amount used should be minimized, and compliance with related laws, regulations, and notifications, including the "Standards for Biological Raw Materials" (Public Notice of the Ministry of Health, Labour and Welfare No. 210 of 2003), should be ensured. In particular, information on virus inactivation and removal should be adequately evaluated, and measures to enable retrospective surveys, etc. should be specified.

(1) Cell culture

[1] Qualification of all ingredients including media, additives (serum, growth factors, antibiotics, etc.), and reagents used in cell processing should be explained, and specifications should be established, as necessary. To qualify each ingredient and establish the specifications, the application route of the final product should be taken into account.

[2] For medium ingredients, the following points should be noted.

a Ingredients and water used in media should be those of high biological purity handled under quality control according to the standards equivalent to those for drugs or raw materials of drugs wherever possible.

b Of ingredients used in media, all, not limited to the main ingredient, should be specified, and the reason for selection and the quality control method, as necessary, should be clarified. Media such as DMEM, MCDB, HAM, and RPMI of which constitutive ingredients are publicly known, and commercial products are generally used may be deemed as single ingredients.

c The final medium preparation comprising all ingredients should be subjected to performance tests for sterility and suitability for the intended culture. In addition, test items potentially necessary for process control should be included in the specifications to ensure appropriate quality control.

[3] Heterogeneous serum and ingredients derived from heterologous or homologous serum should not be used unless they are essential for processing such as cell activation or proliferation. Especially for products that may be used repeatedly, consideration should be given to avoid their use wherever possible. If use of serum is inevitable, actions should be taken to prevent contamination with/transmission of bacteria, fungi, viruses, abnormal prions, etc. from the serum, and processing method, etc. should be investigated to obtain the final product with these agents removed wherever possible.

a The origin of serum, etc. should be specified.

b Efforts should be made to reduce the risk of infection such as avoiding serum from the area where bovine spongiform encephalopathy has been found wherever possible.

c The serum should be appropriately tested for viruses and mycoplasma specific to the animal of origin to rule out contamination with viruses before use.

d Appropriate treatment should be performed to inactivate and remove bacteria, fungi, viruses, etc. to the extent that would not affect activation or proliferation of cells. For example, treatment using heat, filters, radiation, and/or ultraviolet irradiation in combination, as necessary, should be performed to eliminate the risk of potential viral contamination.

e A portion of the serum used should be reserved to monitor cultured cells for viral infection and patients for onset of viral diseases as well as survey production of antibodies against heterologous serum ingredients.

[4] Use of antibiotics should be avoided wherever possible. However, if the use of antibiotics is considered essential in an early manufacturing process, the subsequent processes should be designed to taper the amount wherever possible, and the justification should be presented in terms of scientific reasons, estimated residual amount in the final product, impact on patients, etc. Patients with a history of hypersensitivity to the antibiotics used should be considered ineligible for the concerned therapy. Of note, the use of antibiotics may not be precluded if their adequate removal is demonstrated.

[5] If growth factors are used, appropriate quality control methods such as specifications for purity and potency should be provided to ensure reproducibility of cell culture attributes.

[6] For medium ingredients and other ingredients used for operations potentially present in the final product, those that do not adversely affect the living body should be selected.

[7] If cells derived from different animal species are used as feeder cells, safety should be ensured from the viewpoint of a risk of infections introduced from the different animal species.

(2) Combination with non-cellular or non-tissue ingredients

[1] Quality and safety of source materials other than cells or tissues

If the final product is composed of not only cells or tissues but also source materials other than cells or tissues (matrix, medical materials, scaffolds, supporting membrane, fibers, beads, etc.), information about the quality and safety should be clearly provided.

The information to be provided should be appropriate in consideration of the type and characteristics of the source material concerned, form or function in the final product, and relation to quality, safety, and efficacy evaluation from a viewpoint of the intended clinical indication. If a bioresorbable material is used, necessary tests should be performed for the degradation products.

For the necessary tests, PFSB/ELD Notification No. 0213001, dated February 13, 2003, of the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau,

Ministry of Health, Labour and Welfare (MHLW), "Basic concepts of biological tests necessary for application for marketing (importing) approval of medical devices," should be referred to, and the test results and justification for use of the concerned source material should be presented. Knowledge and information from literature should be utilized reasonably.

[2] Interactions with intended cells or tissues

For interactions with cells or tissues, methods to confirm the following matters and the confirmation results should be presented.

a That non-cellular or non-tissue ingredients do not adversely affect function, proliferation ability, activity, and stability of the cells or tissues necessary for the intended clinical indication.

b Potential effects of interactions with non-cellular or non-tissue ingredients, such as cellular variations, transformation, and dedifferentiation, should be evaluated to the extent possible.

c That interactions with cells do not compromise properties expected for non-cellular or non-tissue ingredients in the intended clinical indication.

[3] Use of non-cellular or non-tissue ingredients to isolate cells or tissues from the application site

If non-cellular or non-tissue ingredients are used to isolate cells or tissues from the application site, the efficacy and safety should be confirmed with reference to the following items.

a Extent of immunoisolation

b Membrane permeation kinetics and pharmacological effects of cell-derived target biological active substances

c Diffusion of nutrients and discharge

d Effects of non-cellular or non-tissue ingredients on area around the application site

(3) If cells are genetically engineered (modified),

If cells are transfected, details on the following matters should be presented.

[1] Information on the structure, origin, acquisition method, and cloning method of the target gene as well as methods for generation, control, and renewal of cell banks

[2] Nature of transgene

[3] Structure, biological activity, and properties of the target gene product

[4] All source materials, properties, and procedures necessary for preparation of the gene transfer component (including the gene transfer method as well as origin, nature, and acquisition method of a vector for gene transfer)

[5] Structure and properties of the gene transfer component

[6] Methods for banking of cells and viruses for preparation of the vector and gene transfer component as well as to control the banks

For a manufacturing method of transfected cells, Chapter 2 in Attachment "Guideline on Ensuring Quality and Safety of Gene Therapy Products" of PAB Notification No. 1062, dated November 15, 1995, of the Pharmaceutical Affairs Bureau, MHW, "Guideline on Ensuring Quality and Safety of Gene Therapy Products" (hereinafter referred to as "Guidelines on Gene Therapy Products") should be referred to. Justification of the setting should be clearly presented in accordance with the addendum to the notification.

It should be noted that separate procedures are required for genetic engineering (modifications) to cells other than "Human cells, etc." or "Cells with differentiation potential or differentiated cells that do not grow into individual organisms under natural conditions," "Viruses," and "Viroids," if applicable, in accordance with the Act on the Conservation and Sustainable Use of Biological Diversity through Regulations on the Use of Living Modified Organisms (Act No. 97 of 2003).

Section 2 Manufacturing process

For manufacture of cell and tissue processed products, etc., the manufacturing method should be clarified and validated for the following items to the extent possible to ensure the consistent quality.

1 Presence or absence of lot configuration and specification of lot

Whether the product is manufactured on a batch basis or not should be clearly stated. If it is manufactured on a batch basis, definition of a batch should be provided.

2 Manufacturing method

The manufacturing method up to release of the final product, including acceptance of cells or tissues as a source material, should be outlined, and the treatment, necessary process control, and quality control should be specified in detail.

(1) Acceptance inspection

For collected cells or tissues to be used as a source material, test and inspection items for acceptance performed according to the type of cells or tissues and intended use (e.g., visual inspection, microscopic examination, collection yield, viability, characterization of cells or tissues, and microbial test) should be specified with the criteria for each item. For application for confirmation, values measured with test samples obtained to date should be presented, and based on them, provisional values should be indicated.

(2) Inactivation and removal of bacteria, fungi, viruses, etc.

Where necessary and possible, the collected cells or tissues to be used as a source material should be subjected to treatment for inactivation or removal of bacteria, fungi, viruses, etc. to the extent that would not affect the cell viability, phenotype, genetic traits, specific functions, other characteristics, or quality. Measures and evaluation methods for the concerned treatment should be specified.

(3) Mincing of tissue, separation of cells, isolation of specific cells, etc.

Methods for mincing of tissue, separation of cells, isolation of specific cells, and washing of them, operations performed during an early phase of the process where the product is manufactured from the collected cells or tissues to be used as a source material, should be specified. For isolation of specific cells, the identification method should be established.

(4) Culture process

If a culture process is included in the manufacturing process, the medium, culture conditions, culture period, yield, etc. should be specified.

(5) Establishment and use of cell lines

Cell lines should be established with understanding of genetic characteristics of the donor. The method of establishment should be clarified and justified to the extent possible.

To maintain uniform and stable quality of cell lines, indicators required to be characterized (cell purity, morphological features, phenotype-specific markers, karyotype, etc.) should be identified, and the criteria should be specified. The maximum passage number up to which cells can proliferate with stability maintained should be presented.

For cell lines, the possibility of tumorigenesis and malignant transformation should be elucidated using appropriate model animals and discussed.

(6) Cell banking

If cells are banked at any stage in the manufacture of cell and tissue processed products, etc., the reason and methods for generation, characterization, storage, maintenance, control, and renewal of cell banks as well as procedures related to other operation processes and tests should be clearly described in detail with justification. PMSB/ELD Notification No. 873, dated July 14, 2000, of the Evaluation and Licensing Division, Pharmaceutical and Medical Safety Bureau, MHW, "Derivation and Characterisation of Cell Substrates Used for Production of Biotechnological/Biological Products" should be referred to.

(7) Measures to prevent mix-up and cross contamination during the manufacturing process

In the manufacture of cell and tissue processed products, etc., prevention of mix-up and cross contamination during the manufacturing process is of importance, and the preventive measures in the process control should be specified.

3 Characterization of processed cells

To investigate changes associated with processing, the processed cells should be analyzed for items, for example, morphological characteristics, growth characteristics, biochemical markers, immunological markers, characteristic produced substances, and other appropriate markers of genotype or phenotype, and functional analysis should be performed as necessary.

As a part of evaluation for appropriateness of the culture period and cell stability, cells cultured for longer than the proposed culture period should be analyzed to rule out unintended changes in the cells.

4 Form and package of final product

The form and packaging of the final product must ensure quality of the product.

5 Consistency of manufacturing method

Before manufacture of cell and tissue processed products, etc., test samples should be subjected to evaluation, which is intended to verify that the manufacturing process delivers individually processed products (lots) that essentially maintain the cell count and cell viability as well as the characteristics (appropriate markers of phenotype, appropriate markers of genotype, functional properties, percent content of intended cells, etc.) in view of the intended use and application method of the product.

If the cryopreservation or cell culture associated with processing extends over a long period of time, sterility tests should be performed periodically to confirm that sterility is ensured.

6 Change of manufacturing method

If a change has been made to the manufacturing method during development, and study results obtained with the pre-change product are included in an application for confirmation or for approval, comparability of the pre- and post-change products should be demonstrated.

Section 3 Quality control of final product

1 General introduction

The overall measures for quality control of cell and tissue processed products, etc. include establishment of specifications for final products, quality control of source materials for each

application to individual patients, validation and consistency control of manufacturing processes, and proper quality control of intermediate products.

The specifications for final products, which can vary depending on the type and nature of the target cells or tissues, manufacturing method, intended use and method of use of each product, stability, available test methods, etc., should be established in full consideration of the potential variations among cells or tissues handled. The establishment should be rational with justification, employing the viewpoint that the intended quality control can be achieved overall when the specifications complement validation and consistency control of manufacturing processes and quality control of intermediate products or vice versa. Of note, the purpose of an application for confirmation is to confirm that the investigational product has no quality problem. Thus, for the quality attributes necessary for post-trial discussion about a relationship between clinical study results and quality, except for essential attributes such as sterility and mycoplasma, the provisional specifications may be established if inevitable, by specifying appropriate variation ranges based on measured values with a small number of test samples. However, quality control methods including the specifications should be enriched and improved as the clinical trial progresses.

2 Quality control method of final product

For final products, necessary and appropriate specifications should be established with reference to the following general quality control items and tests and justified.

For a product not manufactured on a batch basis, each of individual products is subject to quality control, while for a product manufactured on a batch basis, each batch, but not individual products, is usually subject to quality control. In view of the above, specifications and testing methods appropriate for respective manufacturing formats should be established.

(1) Cell count and viability

The count and viability of the cells obtained should be determined in the final product or appropriate in-process material, as necessary. For an application for confirmation, provisional specifications may be established based on measured values with a small number of test samples.

(2) Identification

Identity of the intended cells or tissues should be confirmed based on appropriately selected items, such as morphological characteristics, biochemical markers, immunological markers, characteristic produced substances, and other appropriate markers of genotype or phenotype.

(3) Cell purity

For cell purity, which can be determined based on presence or absence of abnormally proliferating cells other than the intended cells, transformed cells, and contaminated cells, the test items, test methods, and acceptance criteria should be provided as necessary in view of the origin of the intended cells or tissues and manufacturing processes such as culture conditions. For an application for confirmation, provisional specifications may be established based on measured values with a small number of test samples.

(4) Studies for unintended biological active substances derived from cells

If any of the unintended biological active substances derived from cells is expected to have a significant potential effect on safety of the patient depending on its amount in the product, an appropriate permissible limit test should be established. For an application for confirmation, provisional specifications may be established based on measured values with a small number of test samples.

(5) Process-related impurities

Process-related impurities can be defined as substances that (a) are either present in source materials or derived from non-cellular or non-tissue ingredients, medium ingredients, materials, reagents, etc. in the manufacturing process; (b) may exist as contaminants, residues, new products, degradation products, etc. in the product; and (c) are undesirable from the viewpoint of quality and safety (for example, albumin derived from fetal bovine serum and antibiotics). For any of these substances, its presence should be ruled out based on the process evaluation for removal of and results from in-process control tests on the concerned substance or an amount permissible for its presence should be specified with an appropriate test. Selection of the substances to be tested and setting of the acceptance limits should be justified.

For an application for confirmation, provisional specifications may be established based on measured values with a small number of test samples.

(6) Sterility test and mycoplasma test

For sterility of the final product, adequate evaluation using model specimens should be performed in advance to ensure sterility throughout the manufacturing process. The final product should be demonstrated to be sterile (absence of common bacteria and fungi) by test prior to application to the patient. Appropriate mycoplasma test should be performed as well. If results from the sterility test with the final product are obtained only after administration to the patient, measures to be taken when sterility is denied after that should be specified in advance. In this case, the intermediate product should be demonstrated to be sterile by test, and sterility of the subsequent process up to release of the final product should be strictly controlled. If products manufactured through the same process at the same facility have been applied to the other patients, all of them should be demonstrated to be sterile by test. If the product is manufactured on a batch basis and warranted to be hermetically packaged, representative samples may be tested. If the test is required for every application but provides results only after administration to a patient, applicability should be determined based on the latest data, but even in this case, sterility test with the final product must be performed without fail.

Use of antibiotics in cell culture systems should be avoided wherever possible, but if they are used, treatment should be performed to ensure that the sterility test is not affected.

(7) Bacterial endotoxins

The test should be performed with the impact of contaminants in the sample taken into account. The acceptance limit does not have to be always specified based on measured values but may be specified in view of the safety margin on the basis of a single dose of the final product, as defined in the Japanese Pharmacopoeia. The test may be included as in-process control test. In this case, the criteria should be specified in view of the validation results and justified.

(8) Tests of viruses, etc.

If cells to be used are those that have not been banked and may possibly be in the window period and thus have a risk of HBV, HCV, and HIV replications during the manufacturing process, the intermediate product, final product, etc. should be subjected to appropriate tests to rule out presence of viruses, etc. If a biological ingredient is used in the manufacturing process, tests for viruses derived from the concerned ingredient may have to be considered for the final product. However, adventitious introduction of viruses should be ruled out for the original ingredient or in the process evaluation whenever possible.

(9) Primary performance

If the cryopreservation or cell culture associated with processing extends over a long period of time, sterility tests should be performed periodically to confirm that sterility is ensured. For an application for confirmation, provisional specifications may be established based on measured values with a small number of test samples.

(10) Potency assay

If secretion of a specified biological active substance from cells or tissues essentially represents the indication of the cell and tissue processed products, etc., inspection items and specifications for the concerned biological active substance should be established to ensure that the intended effect is exerted as needed. For expression product of the transgene or intended product secreted from cells, specifications in terms of items such as potency and production amount should be established. For an application for confirmation, provisional specifications may be established based on measured values with a small number of test samples.

(11) Mechanical suitability test

For products requiring certain mechanical strength, specifications should be established to confirm the mechanical suitability and durability in consideration of the application site. For an application for confirmation, provisional specifications may be established based on measured values with a small number of test samples.

Chapter 3 Stability of cell and tissue processed products, etc.

Commercialized cell and tissue processed products, etc. or their critical intermediate products should be subjected to appropriate stability studies based on the cell viability and potency, in full consideration of the storage and distribution periods and storage form. Storage conditions and shelf-life should be established and justified. Especially if cryopreservation and thawing are involved, whether freezing and thawing operations have any impact on stability or specifications of the product should be checked. As necessary, the limit of stability should be identified to the extent possible by investigating the long-term stability for periods beyond the respective standard periods of manufacture and storage. However, this does not apply if the product is used immediately after commercialization.

If commercialized cell and tissue processed products, etc. are transported, the container and procedures for transportation (including temperature control) should be specified and justified.

Chapter 4 Nonclinical safety studies of cell and tissue processed products, etc.

For safety-related matters that may require evaluation based on the properties and application method of the product, appropriate animal or *in vitro* studies should be conducted to a scientifically reasonable extent, if technically possible. Non-cellular or non-tissue ingredients and process-related impurities should be evaluated by physicochemical analytical methods but not in animal studies wherever possible.

Human-derived test samples are valuable, and studies of human-derived products in experimental animals do not necessarily yield meaningful results. For this reason, scientific reasonability may be found in studies using study systems where a model product of animal origin is applied to appropriate experimental animals if such studies are considered to yield more useful information. Where appropriate, a cell-based study system may be considered. If a study has been conducted by such an approach, the study system should be justified.

The following are examples of matters to be referred to and points to consider when the safety is non-clinically evaluated as necessary. Again, these are merely examples and not intended to demand conduct of unreasonable studies. Appropriate studies should be considered in view of properties of the product.

1 Confirmation should be made that the cells cultured beyond the culture period have not undergone unintended transformation.

2 Biological active substances such as various cytokines and growth factors produced by cells or tissues should be quantitatively determined as necessary. The effects of their application to the body should be discussed.

3 Potential effects of the product on normal cells or tissues in the recipient patient should be investigated and discussed.

4 Potential undesirable immune reactions to the product and expression product of the transgene should be investigated and discussed.

5 If a cell line is used, the possibility of tumorigenesis and malignant transformation should be elucidated using appropriate model animals and discussed.

6 If the manufacturing process involves transfection with exogenous genes, studies should be conducted in accordance with the Guidelines on Gene Therapy Products. In particular, if viral vector(s) is used, replication-competent viruses should be assessed for an extent of the presence, and the assessment method should be justified.

Descriptions of the transgene and its product should be investigated to elucidate safety. For cells, possibility of proliferative alterations, tumorigenesis, and malignant transformation should be discussed and clarified.

7 If products including model products of animal origin are readily available and potentially provide safety information useful for clinical application, conduct of rationally designed general toxicity studies should be considered.

For conduct of general toxicity studies, the “Guidelines for Toxicity Studies of Drugs,” Attachment to the “Guidelines for Toxicity Studies for Manufacturing (Importing) Approval Application of Drugs” (Joint Notification No. 24 of the First Evaluation and Registration Division, Pharmaceutical Affairs Bureau, MHW, dated September 11, 1989) should be referred to.

Chapter 5 Primary efficacy or performance studies of cell and tissue processed products, etc.

1 Expression of the function, durability of the action, and expected drug or medical device effects of the cell and tissue processed products, etc. should be investigated in appropriately designed studies using experimental animals or cells to the extent technically possible and scientifically reasonable.

2 For transfected cells, the efficiency and durability of expression of the target product from the transgene as well as biological activity and expected drug effects of the expression product from the transgene should be investigated.

3 An appropriate model cell or tissue product of animal origin or disease model animal, if available, should be used to investigate the therapeutic effect.

4 For an application for confirmation, detailed experimental investigations may not always be needed if the therapy using efficacy or performance of the concerned product is expected to

be far superior to the other therapies, and the expectation is reasonably justified by literature or knowledge in and outside Japan.

Chapter 6 Biological disposition of cell and tissue processed products, etc.

1 For cells or tissues constituting the product and expression product of the transgene, studies for the biological disposition such as absorption and distribution in experimental animals should be conducted to the extent technically possible and scientifically reasonable, and based on the results, survival and duration of the action of the cells or tissues in the product applied to the patient should be estimated to show that the intended effect will be adequately obtained.

2 If the concerned cells or tissues are designed to be delivered to a specified site (tissue, etc.) and exert the effect there, the localization should be elucidated.

Chapter 7 Clinical studies

For an application for confirmation, safety evaluation is accompanied by consideration of clinical usefulness. The plan of a clinical trial of cell and tissue processed products, etc. to be conducted in Japan should be assessed in view of the following items.

1 Target disease
2 Definitions of patients eligible for clinical study and those to be excluded from clinical study
3 Details of treatment to be given to subjects, including application of the cell and tissue processed products, etc.
4 Justification of conduct of the clinical study based on comparison with existing therapies
5 Draft matters to be explained to subjects, including risks and benefits expected from currently available information

Clinical studies need to be conducted using appropriately specified design and endpoints and thus should be appropriately planned in view of the origin of the intended cells or tissues, target disease, and application method.