Basic Points to Consider for Cell Storage under the Act on the Safety of Regenerative Medicine

The Japanese Society for Regenerative Medicine

FY 2022 TF Committee on Basic Points to Consider for Cell Storage under the Act on the Safety of Regenerative Medicine

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2. Introduction

2.1. Background

In Japan, the Act on the Safety of Regenerative Medicine (RM Safety Act) came into effect in 2014, regenerative medicine and cell therapies (RMTs) using processed cells without manufacturing and marketing authorization, which are performed as non-commercial clinical trials or as out-of-pocket therapies at the discretion of medical practitioners, have been regulated by this Act. After enforcement of the RM Safety Act, the reality of the provision of RMTs has been gradually elucidated. The Evaluation Committee on Regenerative Medicine, Health Sciences Council has been examining the safety and scientific validity of RMTs as well as strategies for promoting research on RMTs to address a wide variety of technologies for RMTs. One of the issues reviewed by the Committee is the ways of storage of processed cells and their raw materials for RMTs. Because RMTs set forth in the RM Safety Act is medical technology using processed cells, the quality of these processed cells greatly influences the quality and effect of medical technology. The RM Safety Act, however, does not clearly stipulate control standards, operations, or other relevant matters for the storage of processed cells and their raw materials in non-cell processing facilities. As a result, opinions are occasionally raised that these points should be more clearly clarified for appropriate and safe dissemination and advancement of RMTs using autologous and allogeneic cells. In the future, specialized and detailed discussions on the modality of cell storage will be needed in light of its current situation.

Against such a background, as shown in Table 1, the draft of control standards presenting basic matters concerning cell storage were drawn up in the 2019 Health and Labour Sciences Special Research Project, *Research contributing to the establishment of control standards for the storage of processed cells and their raw materials under the Act on the Safety of Regenerative Medicine* (hereinafter referred to “the Research”) in consideration of the current situation provided RMTs which

were mainly on the basis of Article 7 (Acquisition of cells: cells should be appropriately provided or collected from animals, and necessary control should be implemented for the storage of such cells) of Enforcement Regulation of the RM Safety Act. The control standards are applicable to medical practitioners providing RMTs (RMT practitioners) in accordance with the RM Safety Act with the use of human-derived processed cells and their raw materials stored in non-cell processing facilities.

Table 1 The draft of control standard presenting basic matters concerning cell storage [1]

1.	Matters concerning the system of facilities storing human-derived cells used as processed cells and their raw materials
1.1.	Check that a person responsible for controlling and supervising storage operations is designated in a facility to store human-derived processed cells and their raw materials that are separate from the cell processing facilities stipulated under the RM Safety Act.
1.2.	Check that the characteristics, infection risk, and other relevant matters of cells to be kept have been understood, and the keeper can contact and communicate with the entrustor in a facility storing human-derived processed cells and their raw materials that are separate from the cell processing facilities stipulated under the RM Safety Act.
2.	Matters concerning the harvesting of cells and tissue
2.1.	Check that information on traceability and eligibility in terms of the ethics and safety of donors pursuant to Article 7 of the Enforcement Regulations has been obtained from a facility storing human-derived processed cells and their raw materials that are separate from the cell processing facilities stipulated under the RM Safety Act.
3.	Matters concerning the storage of cells (including documents on the cells) that may be of

	the raw materials of RMTs
3.1.	Check that a minimum necessary system has been organized for the control of building and facilities, measures to prevent mix-up and contamination, securing traceability, education and training of personnel, storage procedure, information management, record control, and successive reporting of deviations to the keeper in a facility storing human-derived processed cells and their raw materials that separate from the cell processing facilities stipulated under the RM Safety Act.
3.2.	Check that a means of communication has been ensured for being aware of information (e.g., verification of past medical history, information on physical examination and tests, etc., according to the purpose of use stipulated in Article 7 of the Enforcement Regulations) that will be necessary in the future when clinically using stored human-derived processed cells and their raw materials.
4.	Other matters
4.1.	Matters concerning a system to transfer the stored human-derived processed cells and their raw materials to institutions providing RMTs or cell processing facilities
4.1.1.	Specific requirements for transferring the processed cells concerned to providers (institutions providing RMTs or cell processing facilities) from a facility storing human-derived processed cells and their raw materials that are separate from the cell processing facilities stipulated under the RM Safety Act are determined according to purposes. Check that there is a transfer method ensuring acceptance criteria for human-derived processed cells and their raw materials that are specified by RMT practitioners concerned.

In the Research, it is mentioned that presenting not only the control standards, but also scientific

evidence-based document summarizing technical considerations in cell storage provided by academic societies is important. Consequently, the Task Force for summarization of the Document was established in the Japanese Society for Regenerative Medicine.

2.2. Purpose

The purpose of the Document is to present what RMT practitioners should consider in cell storage as well as what the institution and facility for cell storage should consider, thereby contributing to the appropriate dissemination and advancement of RMTs.

3. Scope

The Document applies to the work of RMT practitioners who intend to store human-derived specified processed cells and/or their raw materials in a frozen state, and the work at institutions that provide cell storage. However, the Document is not applicable to the storage of tissues (e.g., tissues collected at medical institutions and tissues processed including cell culture at cell processing facilities).

4. Glossary

4.1. Primary container

A primary container in the Document refers to a container that has direct contact with cell suspensions.

4.2. Liquid nitrogen container

A liquid nitrogen container in the Document refers to a container that stores liquid nitrogen supplied as a refrigerant in cryopreservation equipment.

4.3. Tight container

A tight container protects the contents from extraneous solids or liquids, from loss of the contents, and from efflorescence, deliquescence, or evaporation under ordinary or customary conditions of handling, shipment, and storage. The definition is cited from *The Japanese Pharmacopoeia 18th edition*.

4.4. Cell storage manager

A cell storage manager in the Document refers to a person who understands the characteristics of stored cells, has adequate knowledge and skills in cell storage, and is responsible for cell storage and the safety of cell storage operators.

4.5. Institution that only provides cell storage

An institution that only provides cell storage in the Document refers to an institution that is used exclusively for storage among institutions that provide cell storage.

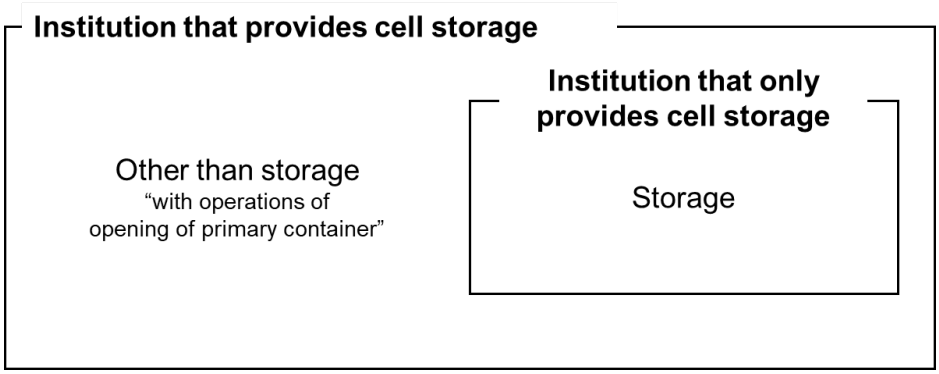

Figure 1 Institution that provides cell storage and institution that only provides cell storage

4.6. Cell storage operator

A cell storage operator in the Document refers to a person who has been trained for cell storage and performs operations to store cells under the cell storage manager. The cell storage manager and cell storage operators are collectively referred to as “cell storage operators, etc.”.

4.7. Institution that provides cell storage

An institution that provides cell storage in the Document refers to an institution that stores cells in a frozen state.

4.8. Cryopreservation equipment

Cryopreservation equipment in the Document refers to equipment for storing cells that can meet predefined storage conditions in a steady state. For example, it includes containers with liquid nitrogen as a refrigerant and electric freezer.

4.9. Cryopreservation container

A cryopreservation container in the Document refers to a container with liquid nitrogen as a refrigerant among cryopreservation equipment.

4.10. Preservation

Preservation in the Document refers to suppressing changes in the characteristics of the cells to a minimum. Conditions enabling realization of preservation are referred to as preservation conditions. For example, they can be preservation conditions such as preservation temperature and being sterile as defined by RMT practitioners.

4.11. Storage

Storage in the Document refers to providing and maintaining an environment not deviating from predefined preservation conditions for cells. Also, conditions enabling realization of storage are referred to as storage conditions. For example, they can storage conditions such as appropriate properties of hermeticity or airtightness and shock resistance for the primary container and to maintain temperature and the refrigerant in the cryopreservation equipment for the cryopreservation equipment.

4.12. Hermetic container

A hermetic container is impervious to air or any other gas under ordinary or customary conditions of handling, shipment, and storage. The definition is cited from *The Japanese Pharmacopoeia 18th edition.*

4.13. Sterile

Free from viable microorganisms. The definition is cited from the *Guidance on the Manufacture of Sterile Pharmaceutical Products by Aseptic Processing*.

5. Requirements for cell storage

For cell storage, it is required to set storage conditions so as not to deviate from the preservation conditions for cells predefined by RMT practitioners and to perform appropriate control and management. RMT practitioners should confirm that proper management of cell storage is feasible in the institution that provides cell storage. However, when RMTs using the stored cells is undecided at the time of its storage, the institution that provides cell storage should define the preservation condition.

At that time, the institution that provides cell storage should make preparations so that information including traceability can be appropriately notified to RMT practitioners using the stored cells and arrange for RMT practitioners using the stored cells to be able to determine whether the stored cells are usable for RMTs.

5.1. Stored cells

Preservation conditions that can suppress change in the characteristics of cells to a minimum should be predefined (e.g., preservation temperature and being sterile). When defining preservation conditions, the relationship between quality of cells and temperature should be adequately understood. It is recommended, as necessary, to confirm that the characteristics of cells are maintained during the anticipated duration of storage beforehand. The preservation conditions should be, in principle, defined by RMT practitioners.

5.2. Primary container

Storage conditions that do not deviate from the preservation conditions for cells should be defined (e.g., to have appropriate properties of hermeticity or airtightness and shock resistance), and primary containers meeting these storage conditions should be selected. The storage conditions for primary containers should be, in principle, defined by RMT practitioners.

5.3. Cryopreservation equipment

Storage conditions that do not deviate from the preservation conditions for cells and the storage conditions for primary containers should be defined, and cryopreservation equipment should be appropriately controlled to meet these storage conditions (e.g., to maintain temperature and the

refrigerant level in the cryopreservation equipment). The storage conditions for cryopreservation equipment should be, in principle, defined by the cell storage manager and confirmed by RMT practitioners.

5.4. Area for the location of the cryopreservation equipment

Storage conditions that do not deviate from the preservation conditions for cells and the storage conditions for primary container and cryopreservation equipment should be defined, an area for the location of the cryopreservation equipment (ALCE) should be appropriately controlled to meet these storage conditions (e.g., to maintain temperature and humidity in the ALCE). The storage conditions for the ALCE should be, in principle, defined by the cell storage manager and confirmed by RMT practitioners.

5.5. Management of the institution that provides cell storage

Appropriate management necessary for control to not deviate from the preservation conditions for cells and the storage conditions for primary container, cryopreservation equipment, and the ALCE, should be performed (e.g., establishment of an organizational system and written procedures including emergency procedures, retention of records and data, implementation of education and training, and ensuring cell storage operators safety).

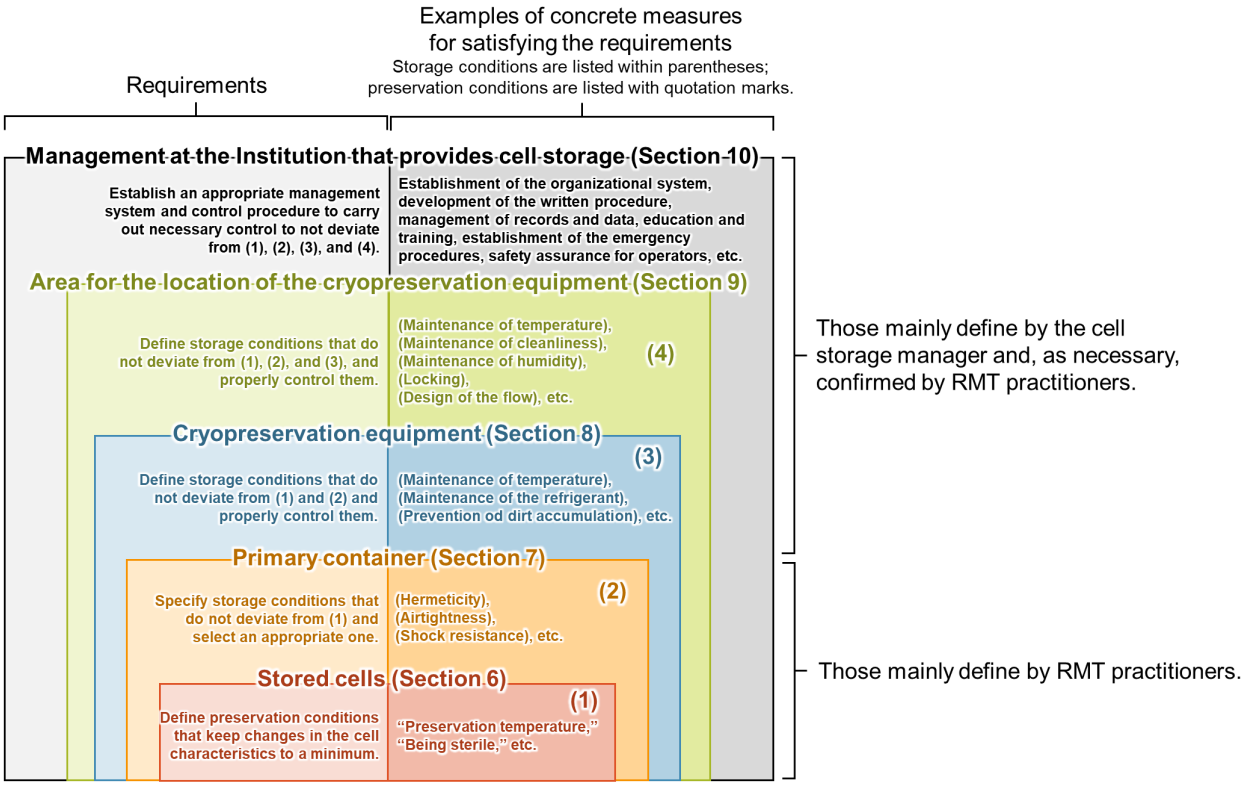

Figure 2 Requirements for cell storage and examples of concrete measures for satisfying them.

6. Basic points to consider for the stored cells

RMT practitioners should define preservation conditions for cells. Examples of preservation conditions, which should be defined in advance, are as follows:

1) Temperatures that minimize changes in the characteristics of cells.

2) Being sterile.

3) Others that RMT practitioners find necessary.

6.1. Basic concept of preservation temperature

It is difficult to maintain the characteristics of cells for a long time because they continuously change their state due to biological reactions such as metabolism. In order to maintain the characteristics of cells over a prolonged period, in principle, it is necessary to stop biological reactions by storing at a temperature below the glass transition temperature (e.g., the glass transition temperature of pure water is approximately -135℃ [2]). Temperatures higher than the glass transition temperature are considered to be at a temperature in which water in a liquid state remains in the primary container and biological reactions are greatly suppressed in a temperature-dependent manner but do not stop [2]. It is understood that the cell state gradually changes, thus the maintenance of their characteristics is difficult during long-term cell storage on a monthly or yearly basis in these temperatures [2]. In contrast, temperatures below the glass transition temperature are considered to be at a temperature at which water in a liquid state does not remain in the primary container and biological reactions stop [2]. Hence, in order to maintain the characteristics of cells for a long time, in principle, it is recommended to define the preservation temperature to below the glass transition temperature. If temperatures higher than the glass transition temperature is defined for the preservation temperature, it is recommended to assess beforehand the effect on the characteristics of cells during the anticipated period of storage to check that the characteristics are maintained.

6.2. Assurance of sterility

It is recommended that RMT practitioners, as necessary, confirm that the sterility of the cells is secured before cell storage.

7. Basic points to consider for the primary container

RMT practitioners should define storage conditions that do not deviate from the predefined preservation conditions for cells and select the primary container that can meet the storage conditions. It is recommended to check that the primary container has the following functions when choosing it:

1) The container is sterilized using gamma irradiation or other relevant methods.
2) The container is a hermetic container or an airtight container. It is recommended, as necessary, to take measures against contamination such as using the outer in combination so that the surface of the container does not have direct contact with the external environment. Examples of other measures for contamination include cell storage in an environment where the control of dirt includes microorganisms in the cryopreservation equipment (see Section "8.1. Control of the cryopreservation equipment") and appropriate cleanliness of the ALCE is carried out (see Section "9.2. Control of the ALCE"), as necessary, upon consultation with the cell storage manager at the institution that provides cell storage.
3) The container is not breakable under the preservation conditions for cells.
4) The container can be labeled so that it is adequately distinguishable. The label should be resistant under the preservation conditions for cells.
5) The container has other functions that RMT practitioners find necessary.

8. Basic points to consider for the cryopreservation equipment

8.1. Control of the cryopreservation equipment

The cell storage manager should define storage conditions that do not deviate from the predefined preservation conditions for cells and the storage conditions for the primary container and appropriately

control the cryopreservation equipment to meet the storage conditions. For implementing the control, written procedures for cryopreservation equipment should be constructed, the control should be carried out in accordance with the written procedures, and records should be prepared as well. In addition, it is recommended to include details of procedures taken in the event of a deviation from the procedure and storage conditions in the written procedure, and to give education and training so that the deviation can be handled accordingly. Examples of the control contents of cryopreservation equipment are those listed below. It is recommended to specify the frequency of inspection by conducting a risk assessment at the institution that provides cell storage.

1) Conduct qualification before using the cryopreservation equipment to confirm that it can meet the predefined preservation conditions for cells and the storage conditions for the primary container.
2) Take actions enabling appropriate measurement of temperature in the cryopreservation equipment and the height of the level of liquid nitrogen in the cryopreservation container. And check that its measurement instruments are properly installed at adequate frequency.
3) Check that the top and door of the cryopreservation equipment are properly closed at adequate frequency.
4) Check that the temperature in the cryopreservation equipment and the height of the level of liquid nitrogen in the cryopreservation container is within the control acceptance criteria at adequate frequency.
5) Calibrate the measurement instruments for the temperature in the cryopreservation equipment and the height of the level of liquid nitrogen in the cryopreservation container at adequate frequency.
6) Construct a procedure to clean the inside of the cryopreservation equipment at adequate frequency as necessary if it is assumed that the sterility of the cells is difficult to maintain because of an

accumulation of dirt including microorganisms in the cryopreservation equipment as a result of opening and closing the top and door of cryopreservation equipment. However, the procedure should be designed in such a manner that the preservation conditions for cells and the storage conditions for the primary container will not be deviated from (see Section “9.2. Control of the ALCE”).

7) Defrost in the cryopreservation equipment appropriately so as not to deviate from the preservation conditions for cells and the storage conditions for the primary container.
8) Prepare equipment to properly provide power in the event of a power outage, as necessary, and appropriately control it when an electric deep freezer is used among cryopreservation equipment.
9) Check other items that the cell storage manager finds necessary at adequate frequency.

8.2. Control of the liquid nitrogen container

When a cryopreservation container is used, the cell storage manager should appropriately control the liquid nitrogen container. For its control, as with the control of cryopreservation equipment, a written procedure for liquid nitrogen containers should be constructed, the control should be carried out in accordance with the written procedures, and records should be prepared as well. In addition, it is recommended to include details of procedures taken in the event of a deviation from the procedure and storage conditions in the written procedure, and to give education and training so that the deviation can be handled accordingly. Examples of the control contents of liquid nitrogen containers are those listed below. It is recommended to specify the frequency of inspection by conducting a risk assessment at the institution that provides cell storage.

1) Take actions enabling appropriate measurement of the remaining amount of liquid nitrogen in the

container. And check the remaining amount at adequate frequency.

2) Take actions such as placing a protective covering so as not to contaminate the workflow when replacing the liquid nitrogen container. Note that dirt attached to the liquid nitrogen container may contaminate the workflow.
3) Check that there is no leakage, such as a spout of nitrogen gas from the connection of the liquid nitrogen container, at adequate frequency.
4) Calibrate the measurement instruments for the remaining amount of liquid nitrogen at adequate frequency.
5) Check other items that the cell storage manager finds necessary at adequate frequency.

9. Basic points to consider for the ALCE

9.1. Establishment of the ALCE

It is recommended to establish the ALCE in a controlled area to which access from the exterior is restricted and only cell storage operators, etc. who have been authorized beforehand can access. In the maintenance operations such as periodic inspection in the institution that provides cell storage, it is recommended to develop a written procedure for the control of the ALCE and to conduct qualification so as not to deviate from the preservation conditions for cells and the storage conditions for the primary container and cryopreservation equipment.

9.1.1. When the ALCE is established in the cell processing facility

In the cell processing facility, it is recommended to establish the ALCE in any part of the work area, and place cryopreservation equipment solely in the ALCE. When it is difficult to establish an independent ALCE, by constructing an appropriate procedure for control, the ALCE and areas where

other operations are performed may be shared. In addition, management such as control of dirt accumulating in the cryopreservation equipment becomes complicated, so it is not recommended to establish the ALCE in an area that is controlled at a sophisticated level of cleanliness. When establishing the ALCE in an area that controlled at a sophisticated level of cleanliness, it is recommended to construct an appropriate procedure for control and conduct qualification to confirm that it does not affect the samples to be handled, operations to be carried out, and their workflow or that the risks are acceptable.

9.1.2. When the ALCE is established in the non-cell processing facility

In the non-cell processing facility, it is also recommended to establish the ALCE and to appropriately control buildings and facilities. When the ALCE is shared with areas where different operations are implemented, it is recommended that continuous feasibility of the control and management of buildings and facilities can be reasonably explained. For restriction of access to the ALCE, it is recommended that the institution that provides cell storage conducts a risk assessment and carries out appropriate control based on anticipated risks, such as locking the ALCE or the cryopreservation equipment or allowing access only by cell storage operators, etc. who are authorized beforehand.

9.2. Control of the ALCE

For the ALCE, storage conditions to not deviate from the preservation conditions for cells and the storage conditions for the primary container and cryopreservation equipment should be defined, the ALCE should be appropriately controlled to meet the storage conditions. For its control, a written procedure for the control of the ALCE should be constructed, the control should be carried out in accordance with the written procedure, and records should be prepared as well. In addition, it is

recommended to include details of procedures taken in the event of a deviation from the procedure and storage conditions in the written procedure, and to give education and training so that the deviation can be handled accordingly. Examples of the control contents of ALCE are those listed below. It is recommended to specify the frequency of inspection by conducting a risk assessment at the institution that provides cell storage.

1) Define and control an appropriate temperature in the ALCE to ensure it does not affect the operations of receiving and shipping stored cells from the cryopreservation equipment.
2) Control humidity in the ALCE, as necessary, when there is a risk of microorganism growth due to dew condensation.
3) Control cleanliness in ALCE, as necessary.
4) Construct procedures that can maintain cleanliness below the control acceptance criteria when liquid nitrogen is supplied in the cryopreservation container.
5) Clean the ALCE at adequate frequency.
6) Measure oxygen concentrations in the ALCE at an appropriate measurement position from the viewpoint of the cell storage operators' safety. And, when the oxygen concentration decreases in the ALCE, take measures that enable the obtainment of such information from outside the ALCE (e.g., placing a monitor outside the ALCE that enables oxygen concentrations to be checked in the ALCE and installing an alarm device).
7) Check other items that the cell storage manager finds necessary at adequate frequency.

10. Basic points to consider for management at the institution that provides cell storage

10.1. Basic concept of management at the institution that provides cell storage

The institution that provides cell storage is required to conduct proper management to execute the necessary control so that there will be no deviation from the preservation conditions specified by the RMT practitioners and the storage conditions for the primary container, cryopreservation equipment, and the ALCE. For the basic idea of the management of cell storage, see also related documents such as the Reference [3] listed in Section “11. References.”.

10.2. Organization and responsible person

The institution that provides cell storage should appoint cell storage operators, etc., and clearly specify them in documents such as a written procedure of cell storage.

10.2.1. Cell storage manager

A cell storage manager is a person who understands the characteristics of stored cells, has adequate knowledge and skills in cell storage, and is responsible for cell storage and the safety of cell storage operators. Examples of the role of the cell storage manager are as follows:

1) Construction and management of the written procedure for cell storage based on a plan for the provision of RMTs. It is recommended that the RMT practitioners approve or confirm the contents of the written procedure for cell storage.
2) Understanding the organization and its implementation status at the institution that provides cell storage where the cell storage manager is working.

3) Assessment as to whether the cells have been stored without deviating from the written procedure for cell storage.

4) Safety assurance and establishment of an education and training system for cell storage operators, etc.

5) Preparation and control of records on cell storage.

6) Establishment of a contact section coordinating with the RMT practitioners.

7) Establishment of an emergency contact system.

8) Establishment of an alternative method of cell storage in case of an emergency.

10.2.2. Cell storage operator

A cell storage operator should receive education and training on cell storage and carry out operations to store the cells under the direction and supervision of the cell storage manager.

10.3. Defining storage conditions

Before cell storage, storage conditions according to the characteristics of the cells should be defined. When examining the storage conditions, the cell storage manager should receive sufficient information on the characteristics of the cells, including the plan for the provision of RMTs from the RMT practitioners, and define appropriate storage conditions with the RMT practitioners. In addition, there may be cells intended to be stored for a short time (e.g., storage until the results of a series of tests are obtained) and for a long time. Thus, an appropriate control procedure to avoid cross-contamination and mix-up, such as separating cryopreservation equipment according to the purposes, should be constructed. Also, transferring the stored cells between the cryopreservation equipment during storage in the institution that provides cell storage without RMT practitioners being aware of the situation

should be avoided because it may affect the characteristics of the cells. Therefore, it is recommended to prespecify the transfer between the cryopreservation equipment during storage, including its acceptability, conditions for, and frequency of transfer as part of the storage conditions.

10.4. Construction of the written procedure for cell storage

The cell storage manager should prepare the written procedure for cell storage and have the cell storage operators, etc. appropriately carry out the cell storage. Examples of the contents to be included in the written procedure are those listed below. When constructing the written procedure, it is recommended to consider warming and re-cooling not only the cells subject to receive and ship, but also other cells not subject to receive and ship in the same cryopreservation equipment. The temperature rise above the glass transition temperature has risks such as the restart of biological reactions in cells and ice crystal regrowth, and it is recommended to construct appropriate procedures considering these risks (see Section 6.1. Basic concept of preservation temperatures).

1) Contents of the procedure for accepting cells (e.g., procedure for acceptance testing, receiving and inventory control).
2) Contents of the procedure for transferring cells from transport containers to cryopreservation equipment.
3) Contents of the periodic inspection and its frequency in the cryopreservation equipment.
4) Contents of the procedure for transferring the cells between cryopreservation equipment.
5) Contents of the procedure for transferring the cells from cryopreservation equipment to transport containers.
6) Contents of the procedure for shipping the cells (e.g., procedure for shipping and inventory

control).

7) Contents of the prevention of the mix-up of the cells, cross-contamination, and microorganism contamination.
8) Contents of the procedure for actions taken for deviations.
9) Other contents that the cell storage manager finds necessary.

10.5. Management of record and data

The cell storage manager should construct procedure records and retain them for a required period of time in accordance with the written procedure for cell storage. Particularly, it is recommended to create a backup for digital data as necessary. Examples of the contents to be recorded are as follows:

1) Contents of the organization at the institution that provides cell storage.
2) Contents of the approved written procedure.
3) Contents of records on education and training (e.g., implementation plan and record).
4) Contents of records on the qualification of cryopreservation equipment.
5) Contents of records on the acceptance of the cells (e.g., appearance testing results, arrival time, and transport temperature).
6) Contents of records cells (e.g., the name of specified processed cells used for RMTs, patient identification number, lot number, quantity, time and date of receiving and shipping, the names of the cell storage operators who received and shipped the cells).
7) Contents of the written request or instruction for storage from RMT practitioners.
8) Contents of records on device control (e.g., records on calibration of measurement devices and validation of thermostats).

9) Contents of records on the results of a variety of monitoring (e.g., temperature in the cryopreservation equipment during storage).

10) Contents of records on deviations from procedures and their corrective measures.

11) Other items that the cell storage manager finds necessary.

10.6. Education and training

The cell storage manager should construct a plan for the education and training necessary for cell storage and provide education and training to the cell storage operators, etc., at adequate frequency.

10.6.1. Education and training personnel

The cell storage manager should appoint education and training personnel for cell storage, have them establish and implement an appropriate system of education and training for the cell storage operators, etc., and verify that education and training have been provided. Note that the cell storage manager may become the education and training personnel.

10.6.2. Contents of education and training

Education and training may be lectures and practical skills concerning the details of factors that affect the cells during storage (e.g., the environment of the ALCE and temperature during storage) and details on the safety of operators (e.g., the potential risk of bacterial and viral infection from the cells). In addition, since liquid nitrogen is used as a refrigerant for the cryopreservation container, actions in accordance with the High-Pressure Gas Safety Act and the Industrial Safety and Health Act (especially the Ordinance on Prevention of Anoxia) and other relevant regulations are required to be taken. Thus, it is recommended to give education on high pressure gas safety and other appropriate educational

programs. Examples of the contents of education and training are as follows:

1) Contents of the characteristics of stored cells, storage purpose and precautions for handling.
2) Contents of the primary container (e.g., the forms of the primary container and outer package, and summary of functions).
3) Contents of precautions for handling high pressure gases such as liquid nitrogen.
4) Contents of the procedures of cell storage (e.g., temperature control, receiving and shipping, and transport procedure).
5) Contents of procedures, reporting system, and recurrence preventive measures in case of an emergency (e.g., equipment failure, accident, disasters, power outage, and leakage of the cells due to breakage of the primary container).
6) Other contents that the education and training personnel find necessary.

10.7. Emergency procedures

It is recommended to predefine cases deemed as emergencies such as natural disasters and accidents by the cell storage manager. Emergencies are circumstances that cause or are anticipated to cause deviations from the predefined preservation conditions for cells and the storage conditions for the primary container, cryopreservation equipment, and the ALCE. It is recommended to define emergencies according to the purpose of storage and the characteristics of the cells. In addition to the storage method, it is also recommended that the cell storage manager discusses beforehand an alternative storage method and actions in case of an emergency with the RMT practitioners. Furthermore, it is recommended to formulate an emergency contact system in advance by the cell storage manager and the system is shared with the RMT practitioners. In a state of emergency, it is

recommended to take action in accordance with the written procedure and contingency manual. Examples of the actions are as follows:

1) Emergency calls to the RMT practitioners and cell storage operators, etc.
2) Prevention of leakage and spread of the cells in the case of storing cells suspected to contain infectious agents.
3) Shift the stored cells to the alternative storage method.
4) Restoration to the usual storage method from the alternative storage method after conclusion of the emergency.

10.8. Transportation of the cells

When the institution that provides cell storage transports the cells for their storage, it is recommended the cell storage manager to specify the transport container and construct the procedures for transportation including temperature control and clarify their validity. For points to note for the transport of cells, see related documents such as the Reference [4] and [5] of Section "11. References" and it is recommended to properly control them.

11. References

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