



Ministry of Health Malaysia



# NATIONAL STANDARDS FOR STEM CELL TRANSPLANTATION:



COLLECTION, PROCESSING, STORAGE AND  
INFUSION OF HAEMOPOIETIC STEM CELLS  
AND THERAPEUTIC CELLS



July 2009 MOH/P/PAK/188.09(BP)



Clinical Support Services Unit  
Medical Development Division  
Ministry of Health Malaysia

# **NATIONAL STANDARDS FOR STEM CELL TRANSPLANTATION: COLLECTION, PROCESSING, STORAGE AND INFUSION OF HAEMOPOIETIC STEM CELLS AND THERAPEUTIC CELLS**

## **TABLE OF CONTENTS**

<b>SECTION 1</b>	<b>INTRODUCTION</b>	<b>4-5</b>
<b>SECTION 2</b>	<b>OBJECTIVES, TERMINOLOGY, ABBREVIATIONS AND DEFINITIONS</b>	<b>6-14</b>
2.1	Objectives	6
2.2	Terminology	6
2.3	Abbreviations	6-7
2.4	Definitions	7-14
<b>SECTION 3</b>	<b>COLLECTION</b>	<b>15-20</b>
3.1	General	15
3.2	The Collection Facility	15
3.3	General Safety Measures	16
3.4	Personnel	16
3.5	Donor/Patient Evaluation and Management	17-18
3.6	Donor/Patient Consents	18
3.7	HSC and TC Collection Procedures	18-19
3.8	Labels of Collection Products	19
3.9	Transportation	19-20
<b>SECTION 4</b>	<b>PROCESSING</b>	<b>21-25</b>
4.1	Laboratory Facilities	21
4.2	Personnel	21-22

4.3 Processing Principles	22
4.4 Types Of Cell Processing	22-23
4.5 Cryopreservation	23
4.6 Labelling	23-25
<b>SECTION 5 STORAGE</b>	<b>26-29</b>
5.1 General	26
5.2 Storage Of Fresh Cells In Liquid State	26
5.3 Storage of Cryopreserved Cells In Frozen State	27-28
5.4 Testing Of Cell Products	28-29
<b>SECTION 6 RELEASE OF PRODUCTS</b>	<b>30</b>
6.1 Facilities	30
6.2 Personnel	30
6.3 Release of Product For Infusion	30
<b>SECTION 7 TRANSPORT OF PRODUCTS</b>	<b>31-33</b>
7.1 General	31
7.2 Transport Within The Collection Facility	31
7.3 Transport Of Fresh Product in Liquid State	31
7.4 Transport Of Cryopreserved Products In Frozen State	32
7.5 Transport Records	33
<b>SECTION 8 INFUSION OF PRODUCTS</b>	<b>34</b>
8.1 Infusion of Products	34
<b>SECTION 9 RETURN STANDARDS</b>	<b>35</b>
9.1 Return of Product From Issue	35
<b>SECTION 10 DISPOSAL STANDARDS</b>	<b>36</b>
10.1 Disposal of Cells No Longer Required For Transplantation of Therapy	36
10.2 Disposal of HSC and TC	36

<b>SECTION 11 RECORDS</b>	<b>37-40</b>
11.1 General Requirements	37
11.2 Electronic Records	37
11.3 Record Maintenance	38
11.4 Records In Case Of Divided Responsibility	40
<b>SECTION 12 QUALITY MANAGEMENT</b>	<b>41-46</b>
12.1 General	41
12.2 Organization	41
12.3 Quality Management System	41
12.4 Document Control	43
12.5 Process Improvement	43
12.6 Personnel	44
12.7 Equipment	44
12.8 Supplies And Reagents	44
12.9 Process Control	45

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**Section 1**  
**INTRODUCTION**

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Stem cells are primitive cells that have remarkable potential to develop into many different cell types in the human body. They possess two important capabilities i.e. self renewal and differentiation. Self renewal is the ability to undergo numerous cycles of cell division while maintaining the undifferentiated state whilst differentiation is a process of cell division as well as commitment to specific cell lineages which eventually mature to various cell types such as blood cells, muscles, nerve, bones and others.

Basically there are two types of stem cells namely embryogenic stem cells (ESC) that are found in a developing embryo and adult stem cells (ASC) that are found in a developed organism. There are significant differences between these two types of stem cells. ESC are capable of developing into any type of cell in the human body i.e. they are pluripotent whilst ASC can develop into a few types of cells and are considered as multipotent. With continuing study in stem cell biology, researchers have recently demonstrated that pluripotent stem cells can be derived from adult fibroblast cultures and thus giving rise to another type of stem cell called induced pluripotent stem cells.

ASC are found in bone marrow, peripheral blood, amniotic fluid and umbilical cord blood. ASC has many potential uses in medical treatment and research. The most established form of utilization of stem cell therapy is haemopoietic stem cell transplantation (HSCT) or commonly known as bone marrow transplantation. HSCT has been used to treat a variety of malignant and non-malignant disorders. The clinical indications have increased over the last thirty-five years, currently include haematological disorders (e.g. leukemia, lymphoma, aplastic anaemia, thalassemia), inherited and acquired immunological disorders and tumour of solid organs such as renal carcinomas. The utilization of ESC remains untested in human being due to safety and ethical issues.

In Malaysia, the current practice of HSCT involves mainly established procedures of HSC transplant and infusion of therapeutic cells such as lymphocytes. Typically a HSCT service consists of clinical management of the patients and several other “more technical or laboratory based”

stages/procedures from collection, processing, cryopreservation, storage and infusion of cells for transplant or therapy. These stages can be undertaken in one or more departments or institutions.

The number of medical institutions and organization providing HSCT service both in the private and government sector is on the increasing trend. In line with Chapter 9 titled “Cell Transplantation” of the **National Organ, Tissue And Cell Transplantation Policy**, these standards are established to promote the standardization of procedures and practices in collection, processing, storage and infusion of haemopoietic stem cells and therapeutic cells among the transplant centres.

These Standards are developed through consensus of specialists and scientists who are actively involved in the HSCT services in Malaysia based on established international standards and guidelines. They are designed to provide minimum guidelines for the procedures stated. Apart from these standards, the laboratory shall comply with relevant national and local regulatory requirements. Thus, compliances to these Standards do not itself confer immunity from legal obligations.

These Standards only focus on the use of internationally established transplant procedures and processes. Those which are still under the investigational list will be addressed in the standards prepared by the National Ethics and Research Committee.

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**Section 2****OBJECTIVES, TERMINOLOGY, ABBREVIATIONS AND DEFINITIONS**

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**2.1 OBJECTIVES**

- 2.1.1 Collection, processing, cryopreservation, and storage of cells for transplantation or therapy involve many stages which can be undertaken in one or more departments or institutions.
- 2.1.2 This document seeks to define the various stages and to propose standards to ensure that a safe and effective product is available for infusion into the recipient. These standards apply to sources of cells currently used for transplantation and cell therapy e.g. bone marrow, peripheral blood and umbilical/placental blood.

**2.2 TERMINOLOGY**

- 2.2.1 For the purpose of these standards, the term shall mean that the standards are to be complied with at all times. The term should indicate an activity that is recommended or advised, but for which there may be effective alternatives.

**2.3 ABBREVIATIONS**

- 2.3.1 The following abbreviations cover terms in the standards.

<i>Ab</i>	Antibody
<i>ABO</i>	Human erythrocyte antigens of the ABO system
<i>Ag</i>	Antigen
<i>BM</i>	Bone marrow
<i>°C</i>	Degrees Celsius
<i>CMV</i>	Cytomegalovirus
<i>COP</i>	College Of Pathologists
<i>CPD</i>	Continuous Professional Development
<i>EBV</i>	Epstein-Barr virus
<i>HAV</i>	Hepatitis A Virus

<i>HBV</i>	Hepatitis B Virus
<i>HCV</i>	Hepatitis C Virus
<i>HIV</i>	Human Immunodeficiency virus
<i>HLA</i>	Human Leukocyte Antigen
<i>HSC</i>	Haemopoietic Stem Cells
<i>HTLV</i>	Human T cell leukemia virus
<i>IATA</i>	International Air Transport Association
<i>ISCT</i>	International Society for Cellular Therapy
<i>JACIE</i>	Joint Accreditation Committee of ISCT-EBMT
<i>MMDR</i>	Malaysian Marrow Donor Registry
<i>NATA</i>	National Association of Testing Authorities, Australia
<i>PB</i>	Peripheral Blood
<i>PBSC</i>	Peripheral Blood Stem Cells
<i>QMS</i>	Quality Management System
<i>Rh</i>	Rhesus antigens on human erythrocytes
<i>SOP</i>	Standard Operating Procedure
<i>TC</i>	Therapeutic Cell
<i>UV</i>	Ultra violet
<i>VZV</i>	Varicella zoster virus

## 2.4 DEFINITIONS

2.4.1 The following abbreviations cover terms in these standards.

### ***Allogeneic***

Refers to haemopoietic stem cell (HSC) and other cells obtained from a donor and intended for infusion into a recipient.

### ***Autologous***

Refers to haemopoietic stem cell (HSC) and other cells obtained from a patient and intended for infusion into that patient i.e. the same person.

### ***Clinical Transplantation Unit***

The unit consists of an integrated health care team headed by a Director, housed in a dedicated space with common staff training programs, protocols and quality assessment systems that meet the National Standards.

***Collection***

Includes any procedure for harvesting haemopoietic stem cell (HSC) or other cell populations regardless of techniques or sources.

***External Proficiency Test***

The use of inter-laboratory comparisons to determine the performance of a laboratory with respect to individual test(s), measurement(s) or observation(s), and to monitor a laboratory's continuing performance.

***Haemopoietic Stem Cells (HSC)***

Include primitive stem cells that are capable of self renewal, multi-lineage differentiation and haemopoietic reconstitution, as well as stem cells that are committed to differentiate along specific lineages.

***Haemopoietic Stem Cells Products (HSC Products)***

Refers to the harvested HSC that is being processed, at any stage of the processing.

***Labelling***

Includes steps taken to identify the original cellular collection, any product components and any product modifications; and to attach the appropriate labels.

***Manipulation***

Refers to an *ex vivo* procedure(s) that enriches, expands or functionally alters cells, or selectively removes particular components from cellular products.

***Mobilisation***

Refers to the administration of drugs or haemopoietic growth factors to a donor or patient in order to increase the number of HSC in the circulation.

### ***Potency***

Refer to the therapeutic activity of a product as indicated by appropriate laboratory tests or adequately developed and controlled clinical data.

### ***Processing***

Refer to all aspects of manipulation, labeling, of products, regardless of source.

### ***Products***

The proper name of each product is as follows:

- Haemopoietic Stem Cells, Apheresis (HSC-A)-haemopoietic stem cells collected from the peripheral blood of a donor or patient using an apheresis technique.
- Haemopoietic Stem Cells, Marrow(HSC-M)- haemopoietic stem cells aspirated from the iliac crests, sternum or other bones of a human donor or patient.
- Therapeutic Cells (TC)-cell products harvested or manufactured for the purpose of providing therapeutic benefit, e.g. lymphocytes, T-cells, mesenchymal cells and dendritic cells.
- Modified Product
  - a) Plasma Reduced-cells remaining after part of the plasma has been depleted by sedimentation or centrifugation using devices, supplies, and techniques validated for the procedure(s).
  - b) RBC Reduced-cells remaining after depletion of mature erythrocytes by sedimentation, centrifugation, or lysis using devices, supplies, and techniques validated for the procedure(s).
  - c) B-Cell-Depleted-cells processed by negative selection for B lymphocytes.

- d) T-Cell-Depleted-cells processed by negative selection for T lymphocytes.
- e) Buffy Coat Enriched- cells remaining after depletion of mature erythrocytes and plasma by sedimentation or centrifugation using devices, supplies, techniques validated for the procedure(s).
- f) Mononuclear cell (MNC) preparations made without density gradient medium are included in this category.
- g) Cryopreserved-cells frozen using devices, supplies, and techniques validated to maintain viability.
- h) Gene-Manipulated cells-cells that have been processed to alter their own genes or introduce new genetic material.
- o Other Target Cell Depletion or Enrichment:
  - a) CD34-Enriched-cells processed by positive selection for CD34-antigen bearing cells.
  - b) Ex Vivo Expanded-cells that have been cultured in vitro for the purpose of producing and/or enriching for a specific functional subset.
  - c) Tumour Cell Depletion- cells processed by negative selection for tumour cells.

***Product Safety***

Refers to relative freedom from harmful effects to persons exposed, directly or indirectly, to a product when administered, taking into consideration the character of the product in relation to the condition of the recipient at the time.

***Quality***

Totality of characteristics of an entity to bear on its ability to satisfy stated and implied needs. For quality definitions, refer to ISO Standard 8402, Quality management and quality assurance-Vocabulary (1994).

***Quality Assurance***

All planned and systematic activities implemented within the quality system, and demonstrated as needed, to provide adequate confidence that an entity will fulfill requirements for quality.

***Quality Control***

Operational techniques and activities that are used to fulfill requirements of quality.

***Quality Improvement***

Actions taken throughout the organization to increase the effectiveness and efficiency of activities and processes in order to provide added benefits to both the organization and its customers.

***Quality Management***

All activities of the overall management function that determine the quality policy, objectives and responsibilities, and implement them by means such as quality planning, quality control, quality assurance and quality improvement within the quality system.

***Routine Processing Procedures***

Refers to services routinely undertaken in the cell processing laboratory including cryopreservation, red cell depletion, buffy coat preparation and density gradient preparation. This list is not exhaustive since new procedures will be introduced from time to time.

a) Plasma Depletion

This refers to the process of removal of plasma from bone marrow, peripheral blood or cord blood cells by sedimentation or centrifugation using devices, supplies and techniques validated for the procedure(s).

b) Red cell Depletion

This refers to the process of removal of mature erythrocytes from human marrow, peripheral blood or cord blood cells by sedimentation or centrifugation using devices, supplies and techniques validated for the procedures(s).

b) Buffy Coat Preparation

This refers to centrifugal separation of the starting product into cellular and plasma products. Indications include blood group incompatibility in allogeneic transplantations or volume reduction in autologous collections.

***Specialised Processing Procedures***

Refers to procedures that are not included above, some of which may be regarded as investigational e.g. Gene manipulation and insertion. The following list is not exhaustive and may be expanded in future. Appropriate institutional review board or human research ethics committee approval for individual projects shall be obtained.

a) Positive Selection

This refers to procedures that select and retain a particular cell type. These include immune-adsorption and immune-magnetic separation procedures.

b) Negative Selection

This refers to procedures that select and remove a particular cell type. These include physico-chemical (e.g. UV irradiation, elutriation, hyperthermia), immunological (e.g. immune-adsorption, immune-magnetic separation, immune-toxin killing, complement lysis) and pharmacological (e.g. 4 hydro-peroxy-cyclophosphamide) purging techniques.

c) Cell Culture and Expansion

This refers to procedures that modify the HSC or other cell preparation by culture and ex vivo stimulation with haemopoietic growth factors, cytokines and stroma.

d) **Gene Manipulation**

This refers to procedures that introduce or modify one or more genes into one or more populations of cells, for the purpose of tracking a particular population of cells following transplantation, or producing specific therapeutic effect(s) through modulation of gene expression in cells.

***Standard Operating Procedures (SOP)***

A compilation of written instructions required to perform all procedures in the facility.

***Syngeneic***

Refers to HSC or other cells obtained from a donor genetically identical to the patient and intended for infusion to that patient.

***Time of collection***

Refers to the end of the haemopoietic cell collection procedure.

***Transplant***

For the purposes of documentation a transplant refers to a single planned episode of treatment. This may include the use of more than one infusion of cellular material as part of that planned episode of treatment.

***Transplantation***

Refers to the infusion of autologous, syngeneic or allogeneic HSC or other TC products with the intent of providing transient (during cytotoxic therapy) or permanent engraftment or in support of therapy of disease.

***Unmanipulated cellular products***

Refers to HSC or TC products obtained at the time of collection and not subjected to any form of manipulation.

***Validation***

Refers to establishing documented evidence that provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specifications and quality attributes. A process is validated to evaluate the performance of a system with regard of its effectiveness based on intended use.

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**Section 3****COLLECTION STANDARDS**

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**3.1 GENERAL**

- 3.1.1 The following standards will apply to HSC and TC collection practices. The National Standards for Cord Blood Banking shall apply to cord blood banking services.

**3.2 THE COLLECTION FACILITY**

The following facilities and service shall be made available:

- 3.2.1 An adequate and confidential space for donor examination and evaluation.
- 3.2.2 A 24 hour emergency and intensive care medical services.
- 3.2.3 A designated area for appropriate preparation and storage of the consumables, reagents and equipments needed for performing the collection procedure.
- 3.2.4 A formal arrangement with an accredited laboratory to perform all the tests required. Refer Section 3.5.7.
- 3.2.5 An appropriately equipped and staffed operating theatre.
- 3.2.6 A transfusion facility or blood bank providing 24-hour blood component support including irradiated blood components and components suitable for CMV-negative recipients.

**3.3 GENERAL SAFETY MEASURES**

- 3.3.1 Each collection facility shall be operated in a manner to minimize risks to the health and ensure safety of donors, patients and employees.
- 3.3.2 There shall be procedures to ensure biological, chemical and radiation safety and monitoring system to ensure compliance.
- 3.3.3 HSC and TC collections shall be handled and discarded with standard universal precautions measures.

**3.4 PERSONNEL AND TRAINING**

- 3.4.1 The HSC and TC cell collection facility shall be led by a Collection Facility Director (however named) with adequate numbers of trained supporting personnel.
- 3.4.2 The Collection Facility Director
  - 3.4.2.1 Shall be a medical specialist with at least one year training and one year experience in HSC and TC collection procedures.
  - 3.4.2.2 Directly responsible for the medical care of patients or donors undergoing the procedure.
  - 3.4.2.3 Responsible for pre-collection evaluation, performance and supervision of the procedure and post-collection management.
  - 3.4.2.4 Shall demonstrate CPD activities in the field of HSC and TC collection and transplantation.
- 3.4.3 All other personnel shall be adequately trained, be involved in CPD activities and maintain competency in HSC and TC collection procedures.

### **3.5 DONOR/PATIENT EVALUATION AND MANAGEMENT**

- 3.5.1 The donor and patient safety shall always be maintained.
- 3.5.2 Both the potential for disease transmission from the donor to recipient and the risk to the donor/patient from the collection procedure shall be assessed.
- 3.5.3 Donor evaluation and laboratory test results shall be documented and any abnormal findings reported to the donor and recommendations made for follow-up care.
- 3.5.4 The use of a donor not meeting the ideal donor criteria shall require documentation of the rationale for his/her selection and informed consent taken from both donor and recipient.
- 3.5.5 Relevant donor medical history including vaccination, blood transfusions and risk assessment for blood borne virus infection, physical examination, psychosocial evaluation and laboratory tests shall be performed and findings documented before initiation of the recipient's preparative regimen.
- 3.5.6 Obstetric history shall be taken and pregnancy test for donors of child-bearing age shall be performed.
- 3.5.7 Laboratory test required for donor selection shall be done by accredited laboratory and include at least the following:
  - 3.5.7.1 HLA-A, B, DR typing and other appropriate compatibility tests as indicated by an accredited laboratory.
  - 3.5.7.2 ABO group and Rh type. Anti-A and Anti-B titre where appropriate.
  - 3.5.7.3 Infectious disease screening shall minimally include the following: HIV-1, HIV-2 HBV, HCV, CMV and syphilis. Where appropriate, additional test for HTLV-1, HTLV-2, EBV, HAV, VZV, HSV-I, HSV-II, toxoplasmosis and cryptosporidium may be performed.
- 3.5.8 In the case of more than one collection from the same donor more than 30 days apart, the test listed in 3.5.7.3 shall be repeated prior to each collection.

- 3.5.9 Donor/Patient fitness for HSC and TC collection shall be documented.
- 3.5.10 PBSC and TC donor shall be evaluated for the risk of apheresis donation with regards to adequate arterial or venous access and the use of growth factors.
- 3.5.11 If haemopoietic growth factor is utilized, its administration shall be under the supervision of a medical practitioner experienced in the management of persons receiving these agents.

### **3.6 DONOR/PATIENT CONSENTS**

- 3.6.1 Informed consent from the donor /patient shall be obtained.
- 3.6.2 The donor/patient shall be informed of the significant risks and benefits of the procedure, tests performed to protect the health of the donor and recipient and their rights to review the results of their tests.
- 3.6.3 The donor shall be given the opportunity to ask questions and the right to refuse to donate.
- 3.6.4 In the case of a donor below the age of consent, informed consent shall be obtained from the donor's parents or legal guardian.
- 3.6.5 If the donor's name is to be added to a HSC donor registry, informed consent shall be obtained and documented.

### **3.7 HSC AND TC COLLECTION PROCEDURES**

- 3.7.1 Documentation for donor evaluation, selection and consent shall be available prior to collection procedures.
- 3.7.2 Methods for collection of HSC and other TC shall use validated SOPs approved by the Collection Facility Director.

- 3.7.3 Before collection of HSC and TC; there shall be a written plan regarding timing, procedural details and goals of collection.
- 3.7.4 All reagents and disposables used for collection shall be sterile and Lot numbers and expiry dates recorded.
- 3.7.5 The collected cells shall be packaged in closed sterile bag and shall be labeled accordingly.
- 3.7.6 Marrow cells shall be filtered to remove particulate material prior to final packaging, distribution or transplantation using sterile filters that are non-reactive with blood. **Leukodepletion filters shall not be used.**

### **3.8 LABELS OF COLLECTION PRODUCT**

#### **3.8.1 Product Identification**

3.8.1.1 Each product shall be assigned a unique numeric or alphanumeric identifier by which it will be possible to relate any product to its donor, the donor's medical record, and to all records describing the handling and final disposition of the product.

3.8.1.1.1 There shall be a system of identifying each containers divided from a single product.

3.8.1.2 Labelling at the end of collection shall occur before the container is removed from the proximity of the donor/patient.

3.8.1.3 At the end of collection in the operating room or apheresis unit, the label on the primary container shall bear information as listed in **Table 1: List Of Types of Labels (Appendix 1).**

### **3.9 TRANSPORTATION**

- 3.9.1 Procedures for transportation of freshly collected cells shall be designed to protect the integrity of the product being transported and the health and safety of personnel.
- 3.9.2 The specification of the product packaging and transport container.
  - 3.9.2.1 The product bag shall be made of material approved for the storage of human blood cells.
  - 3.9.2.2 The product bag shall be sealed in a manner that minimizes the risk of cell loss and microbial contamination.
  - 3.9.2.3 Where feasible, the product bag shall then be placed in at least one sealed plastic container.
- 3.9.3 The specification of the transport container.
  - 3.9.3.1 The transport container shall be of an appropriate type to ensure safety and integrity of the product during transport.
- 3.9.4 The temperature during transport shall be maintained at the indicated storage temperature for the product and transported to the processing laboratory as soon as possible.
- 3.9.5 The product shall not be exposed to any source of irradiation.

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**Section 4**  
**PROCESSING STANDARDS**

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**4.1 LABORATORY FACILITIES**

- 4.1.1 The facility responsible for processing and storage of cells shall be of adequate space and design for the intended purposes.
- 4.1.2 There shall be adequate equipment for the procedures performed at the facility.
- 4.1.3 The facility shall be maintained in a clean and orderly manner and not to be used for purposes other than those designated.
- 4.1.4 The facility shall be secured to prevent the admittance of unauthorized personnel.
- 4.1.5 Laboratory equipment is not to be used for microbial cultures or non-patient related work involving cell lines or genetically altered cells.

**4.2 PERSONNEL AND TRAINING**

- 4.2.1 The Processing Laboratory shall be led by a Laboratory Director (however named) with adequate numbers of trained and competent supporting personnel.
- 4.2.2 The Laboratory Director
  - 4.2.2.1 Is a medical specialist with appropriate qualification and postgraduate training in HSC processing and/or transplantation procedures.
  - 4.2.2.2 Shall be responsible for all medical, administrative and technical operations of the cell processing facility, including compliance with these Standards.
  - 4.2.2.3 Should participate regularly in educational activities related to the field of HSC processing and/or transplantation.
- 4.2.3 The Laboratory Quality Manager
  - 4.2.3.1 Shall be designated by the Laboratory Director to establish and maintain systems to review, modify as necessary, and approve all procedures intended to

monitor compliance with these Standards and/or the performance of the facility.

4.2.3.2 Should participate regularly in educational activities related to the field of HSC processing, transplantation and quality management.

4.2.4 All other personnel shall be adequately trained, be involved in CPD activities and maintain competency in HSC and TC processing procedures.

### **4.3 PROCESSING PRINCIPLES**

4.3.1 There shall be a written request to the laboratory from the recipient's transplant physician before collection is begun or processing is initiated.

4.3.2 The procedure for processing of cells shall be performed according to protocols defined in the facility's SOP.

4.3.3 Methods of processing shall employ aseptic techniques and be validated to result in acceptable cell viability and recovery.

4.3.4 Detailed worksheets shall be available and maintained for all procedures.

4.3.5 The objectives and acceptable end-points for each procedure shall be specified.

4.3.6 The Laboratory Director or designee shall review the processing record for every product.

4.3.6.1 The appropriate transplant physician shall be notified of the results of all procedures performed.

4.3.6.2 Notification and appropriate remedial actions, if taken, shall be documented in the processing record.

4.3.7 All instruments and equipment used in the collection, processing, manipulation and quality testing of cell products shall be subject to regularly scheduled cleaning, maintenance and calibration.

4.3.8 A record shall be kept of lot numbers and expiry dates of reagents and disposables used in processing.

### **4.4 TYPES OF CELL PROCESSING**

4.4.1 Routine Processing

4.4.1.1 These are procedures regularly undertaken in transplant facilities. Section 2.4 applies.

4.4.2 Specialised Processing

4.4.2.1 Procedures mentioned in Section 2.4 apply. Investigational procedures shall only be performed as part of a research project.

## 4.5 CRYOPRESERVATION

4.5.1 Protocols

4.5.1.1 The laboratory shall have SOP for cryopreservation addressing the following:

- a) cellular product;
- b) cryoprotectant solution and its final concentration;
- c) cell concentration;
- d) cooling rate;
- e) end point temperature of cooling; and
- f) storage temperature.

4.5.2 Samples

4.5.2.1 Sample aliquots of the product, cryopreserved and stored under the same conditions as the product, should be available for testing as necessary.

## 4.6 LABELLING

4.6.1 General Requirements

4.6.1.1 Labelling of cell products shall be done individually and separately to avoid mislabeling

4.6.1.2 The labelling shall be clear, legible and restricted to areas of the container not in direct contact with the product.

4.6.1.3 The label shall be firmly attached to the container. It shall not obscure other labels or the contents to the extent that the latter cannot be seen or inspected.

4.6.1.4 If the identification is handwritten, the ink shall be permanent and able to withstand fading and disfigurement during processing, transport and storage.

4.6.1.5 Production, storage and distribution of labels shall be controlled to prevent unauthorised access to and issuance of labels, and there shall be procedure for the discard of unused labels.

## 4.6.2 Product Bag Label

### 4.6.2.1 Upon completion of processing,

4.6.2.1.1 the product shall be labelled as a minimum (partial label) with the following:

- a) the proper name of the product;
- b) the unique identifier of the product;
- c) the name and identifier of the intended recipient, if known.

### 4.6.2.2 Before Release/Issue To A Transplant Centre

4.6.2.2.1 The final label on the product bag(s) shall show the following:

- a) type and proper name of product.
- b) unique product identification number;
- c) donor ID number;
- d) name and other identifications if the intended recipient, if known;
- e) volume in container with an accuracy of +/- 5%;
- f) recommended storage condition(s).

### 4.6.2.3 Minimum Label (partial Label)

4.6.2.3.1 If the container is capable of bearing only partial label, the product bag(s) shall show as a minimum:

- a) the proper name of the product;
- b) the unique identifier of the product;
- c) the name and identifier of the intended recipient, if known.

### 4.6.2.4 At Time Of Release/Issue To A Transplant Centre

4.6.2.4.1 The product bag(s) bearing a partial label shall be enclosed in a sealed package containing the full information in Section 4.6.3 or the full information is securely attached on a tie tag.

### 4.6.2.5 Documentation to Accompany Product

4.6.2.5.1 A product infusion form shall be completed for each product to be infused.

4.6.2.5.2 A copy of this form shall be placed in the recipient's chart after infusion of the product

4.6.2.5.3 This form should include:

- a) all of the information listed in Section 4.6.2.1 and Section 4.6.2.2,
- b) the time the infusion was started, and
- c) the initials of the medical staff involved with the infusion.

#### 4.6.3 Transport Container

4.6.3.1 The transport container shall be labelled or tagged.

4.6.3.2 The information shall include:

- a) name and address of the receiving institution;
- b) the name of the contact person responsible for the handling and receipt of the product at the receiving institution;
- c) the phone number(s) through which the contact person may be reached in the event of a delay or emergency;
- d) a distinctive label: 'DO NOT IRRADIATE, DO NOT X-RAY, BIOHAZARDOUS MATERIAL'; and
- e) name and address of the consigner.

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**Section 5**  
**STORAGE STANDARDS**

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**5.1 GENERAL**

- 5.1.1 Each facility shall establish policies for the duration, conditions of storage and indications for discard.
- 5.1.2 Patient, donors, and associated transplant centres should be informed about the policies prior to HSC collection.
- 5.1.3 There shall be a system of quarantine for all material to ensure that it cannot be released for issue until approved documentation indicates that it conforms to the requirements of use.
- 5.1.4 Product storage facilities shall be secured to ensure that quarantined or released products cannot be tampered with or removed by unauthorised persons.
- 5.1.5 Product storage facilities should not be used for any other purposes.

**5.2 STORAGE OF FRESH CELLS IN LIQUID STATE****5.2.1 General**

- 5.2.1.1 Cells stored in a liquid state shall be maintained at a temperature and for a period of time specified in a protocol validated by the laboratory.

**5.2.2 Storage Duration/Expiry Date**

- 5.2.2.1 If storage cannot be avoided, the temperature and duration of storage should be according to the following guidelines:
  - (a) Storage and transportation at 20 to 24°C. It is recommended that products should be infused or further processed in less than 48 hours after collection.

- (b) Storage and transport at 2 to 6°C. It is recommended that products should be infused or further processed in less than 72 hours after collection.

### **5.3 STORAGE OF CRYOPRESERVED CELLS IN FROZEN STATE**

#### 5.3.1 General

5.3.1.1 Storage shall be within a temperature range-  
80°C to -196°C as determined to be appropriate for the cryoprotectant used.

5.3.1.2 Storage system should be designed to minimise the potential for  
microbial cross-contamination.

#### 5.3.2 Storage Facilities

5.3.2.1 The storage device shall be located in a secure area.

5.3.2.2 Locking capability is recommended but emergency access should be  
available.

#### 5.3.3 Monitoring Systems

5.3.3.1 Refrigerators and freezers for product storage shall have a system to monitor  
and record the temperature continuously. This is best done with an automated  
system but manual check is also acceptable.

5.3.3.2 Liquid nitrogen freezers shall have a system to monitor liquid nitrogen levels. An  
automatic fill mechanism is recommended.

#### 5.3.4 Alarm System

5.3.4.1 Storage devices shall have alarm systems that are continuously active.

5.3.4.2 Alarm systems shall have audible signals.

5.3.4.3 If laboratory personnel are not always present in the immediate area of  
the storage device, a remote alarm device shall be required at a location  
staffed 24 hours a day.

5.3.4.4 The alarm system shall be checked and tested regularly and records shall  
be kept.

#### 5.3.5 Backup Storage Devices

5.3.5.1 Additional storage devices of appropriate temperature shall be available  
for product storage if the primary storage device fails.

5.3.6 Procedures in Case of Failures of Storage Devices

5.3.6.1 There shall be a written procedure to be followed if the storage device fails.

5.3.6.2 This procedure shall be displayed in the immediate area containing the storage device.

5.3.6.3 A procedure for notifying laboratory personnel shall be placed at each remote alarm location and in the immediate area of the storage device.

5.3.7 Inventory Control

5.3.7.1 There shall be an inventory control system to identify the location of each product and associated sample aliquots must be in use.

5.3.7.2 The inventory control system record shall include:

- a) Donor name or identifier
- b) Patient name or identifier
- c) Product unique identifier
- d) Product or specimen proper name
- e) Date of collection
- f) Storage device identifier
- g) Location within storage device
- h) Dates of issue
- i) Disposition

**5.4 TESTING OF CELL PRODUCTS**

5.4.1 Testing of Products For Routine Processing

5.4.1.1 The laboratory shall define tests and procedures for measuring, assaying or monitoring properties of the cell products essential to the evaluation of their safety and usefulness.

5.4.1.2 Results of all such tests and procedures shall become part of the permanent record of the material processed.

5.4.1.3 As a minimum, the following test shall be performed:

- a) Nucleated Cell Counts

A nucleated cell count shall be performed for any product after collection and after any subsequent processing.

- b) CD34+ Cell Counts

- CD34+ cell count and/or other stem cell assays shall be performed on the final peripheral blood stem cell product and ideally harvested bone marrow products.
- target CD34+ cell or nucleated cell count should be determined for each product and monitored against transplant outcomes.

c) Microbial Testing

- cell collection and processing facilities shall perform and document microbial testing of HSC or TC products after collection and post processing.
- the results of microbial cultures shall be reviewed by the Laboratory Director or designee in a timely manner.
- The recipient's transplant physician shall be notified in a timely manner of any positive microbial cultures.

d) ABO/Rh Group Tests

Where applicable, tests for ABO and Rhesus groups shall be performed.

e) Viability Testing

Viability Testing shall be performed on post processing and post thawing.

5.4.1.4 Testing by Outside Laboratories

5.4.1.4.1 Tests required by these standards, not performed by the cell collection or laboratory facility, shall be performed in an accredited laboratory.

5.4.2 Testing of Products for Specialised Processing

5.4.2.1 For products undergoing specialised processing as mentioned in Section 4.4.2, a relevant and validated assay, where available and applicable, for the target population of cells being selected before and after the processing shall be performed in addition to those required in Section 5.4.1.

5.4.3 Time to Engraftment

5.4.3.1 Documentation and review of time of engraftment after cell infusion shall be a part of ongoing quality management.

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**Section 6****RELEASE STANDARDS**

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**6.1 FACILITIES**

6.1.1 Clinical facilities shall meet the requirement of the National Standards and the laboratory facilities shall meet the requirements as in Section 4.1.

**6.2 PERSONNEL AND TRAINING**

6.2.1 Clinical personnel shall meet the requirement of National Standards and the laboratory personnel must meet the requirements as in Section 4.2.

**6.3 RELEASE OF PRODUCTS FOR INFUSION**

6.3.1 Appropriate arrangements shall be made prior to issue of the cellular products to minimize the time between issue and infusion.

**6.3.2 Identification**

6.3.2.1 All labeling requirements shall comply with Section 4.6.

6.3.2.2 The product infusion form shall contain information as mentioned in Section 4.6.2.1 and Section 4.6.2.2.

**6.3.3 Inspection of Product Prior to Release**

6.3.3.1 Each product issued for infusion shall be inspected by two trained personnel immediately before release to verify recipient information and integrity of the product container.

6.3.3.2 The laboratory director shall discuss with the head of clinical transplantation service who shall decide whether for use or to be rejected when the container is compromised and /or recipient's information is not verified.

- 6.3.3.3 A procedure to deal with the splitting or bursting of a product bag shall be established.
- 6.3.3.4 Such accidents shall be reported immediately to the Laboratory Director who shall discuss the matter with the transplant physician to decide whether to reject the bag or administer antibiotics with the bag.
- 6.3.3.5 An aliquot of the specimen shall be sent for sterility check.

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## **Section 7**

### **TRANSPORTATION STANDARDS**

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#### **7.1 GENERAL**

- 7.1.1 Transport of cellular products shall comply with relevant local and international regulations e.g. *Akta Pencegahan Dan Pengawalan Penyakit Berjangkit 1998* and IATA Dangerous Goods Regulations.

#### **7.2 TRANSPORT WITHIN THE COLLECTION FACILITY**

- 7.2.1 Procedures for transportation of fresh and/or cryopreserved products within the collection facility shall be designed to protect the integrity of the product and the health and safety of personnel.

#### **7.3 TRANSPORT OF FRESH PRODUCT IN LIQUID STATE**

- 7.3.1 The temperature during transport shall be maintained at the indicated storage temperature for the product, as specified by the processing laboratory.
- 7.3.2 For Products stored at 2 to 6°C, wet ice may be used
- 7.3.3 Dry ice shall never be used.
- 7.3.4 The specimen shall not be frozen or placed near heat.
- 7.3.5 Packaging and Transport Container Design (please refer to Section 3.9).
- 7.3.6 Outer Shipping Container:
- a) shall be thermally insulated;
  - b) should be made of material adequate to withstand leakages of contents, shocks , pressure changes, and other conditions incident to handling in transportation;

- c) should contain adequate non-particulate absorbent material to contain the entire volume of the primary product container;
- d) shall be labelled as “Medical Specimen” and “Do not X-Ray”;
- e) shall have a biohazard label applied;
- f) shall have the name and address of the receiving facility, the name, room number and phone number of the receiving laboratory if applicable and the name of the responsible person at the receiving facility;
- g) shall have the name, address and phone number of the sender, and the name of the person responsible for the shipment; and
- h) shall have a description of the contents, including the number of containers and volumes in each.

#### 7.3.7 Temperature During Transport

7.3.7.1 The temperature during transport shall be maintained at the indicated storage temperature for the product, as specified by the processing laboratory.

7.3.7.2 The method for maintaining the indicated temperature for the duration of transport shall be validated.

#### 7.3.8 Method of Transport

7.3.8.1 Fresh products shall be hand-carried by a suitably informed courier in the passenger compartment.

7.3.8.2 The products shall not be passed through X-Ray irradiation devices designed to detect metal objects. If inspection is necessary, the content of the container shall be inspected visually.

#### 7.3.9 Transit Time of Product

7.3.9.1 The transit time should be minimised.

7.3.9.2 It is recommended that the total time between cell collection and infusion, including travel time, should not exceed 48 hours.

7.3.9.3 There shall be plans for alternate transport in the event of delay.

### **7.4 TRANSPORT OF CRYOPRESERVED PRODUCTS IN FROZEN STATE**

7.4.1 The shipping container shall conform to the regulations regarding the mode of transport.

- 7.4.2 The shipping container shall be of appropriate design and construction for transportation of the cryogenic material used.
- 7.4.3 Cryopreserved products with an indicated storage temperature below -80°C shall be shipped in liquid nitrogen 'dry shipper' that contains adequate adsorbed liquid nitrogen to maintain temperature for at least 48 hours beyond the expected time of arrival at the receiving facility. Unabsorbed liquid nitrogen shall not be used.
- 7.4.4 The sending facility shall include a temperature monitor in the shipper.
- 7.4.5 The receiving facility shall verify the temperature upon arrival.
  
- 7.4.6 Method of transport
  - 7.4.6.1 Cryopreserved products shall be transported in cargo compartments. A dry shipper which is securely strapped in an appropriate vehicle.
  - 7.4.6.2 The products shall not be passed through X-Ray irradiation devices designed to detect metal objects. If inspection is necessary, the content of the container shall be inspected visually.
  - 7.4.6.3 There shall be plans for alternative transport in an emergency.

## **7.5 TRANSPORTATION RECORDS**

- 7.5.1 Transport records shall permit tracing of the product from the donor to the recipient.
- 7.5.2 Transport records shall identify the source facility and the personnel responsible for shipping the product.
- 7.5.3 Transport records shall document the identity of the courier and any delays or problems occurring during transportation of the product.

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**Section 8**  
**INFUSION STANDARDS**

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**8.1 INFUSION OF PRODUCT**

8.1.1 Inspection of Product Prior to Infusion

8.1.1.1 Each product issued for infusion shall be inspected by two trained personnel immediately before infusion to verify recipient information and integrity of the product container.

8.1.1.2 The head of clinical transplantation service shall give specific authorisation for use when the container is compromised and/or recipient's information is not verified.

8.1.2 Products shall be infused as soon as possible after processing or thawing.

8.1.3 Products containing visible clumps should be infused through a blood administration filter of equal to or greater than 170 micron pore size.

8.1.4 **Leukodepletion filters shall not be used.**

8.1.5 The laboratory shall provide a written form to be completed for product issued containing at a minimum the name and unique identifier, and the initials of the medical staff receiving the product.

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**Section 9**  
**RETURN STANDARDS**

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**9.1 RETURN OF PRODUCT FROM ISSUE**

9.1.1 Products accepted for return shall meet the following conditions:

- a) The integrity of the primary container has not been compromised subsequent to issue from the laboratory
- b) The product has been maintained subsequent to issue at the specified temperature range during storage and transportation.

9.1.2 If the conditions in Section 8.1.1 have not been met, the Laboratory Director shall give specific authorization to accept the products for return and in consultation with the patient's transplant physician who shall authorize reissue or discard of the product.

9.1.3 Products to be reissued shall be inspected and labelled as per Section 4.6.

9.1.4 Documentation of the events requiring return, the results of inspection upon return, and subsequent action taken to ensure product safety and viability until potential reissue shall be maintained in the laboratory record.

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**Section 10**  
**DISPOSAL STANDARDS**

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**10.1 DISPOSAL OF CELLS NO LONGER REQUIRED FOR  
TRANSPLANTATION OR THERAPY**

10.1.1 There shall be a written policy for disposal of haemopoietic stem cell products.

10.1.2. There shall be a written agreement between the patient or designated recipient and the storage facility defining the circumstances for disposal or transfer of cells.

10.1.3 If patient is still alive his/her written consent shall be obtained and if consent is denied, the patient shall be given the opportunity to ship the product to another facility.

**10.2 DISPOSAL OF HSC AND TC:**

10.2.1 Required Documentation

10.2.1.1 There shall be written documentation of patient death or no further need for the product before any product is discarded.

10.2.2 Approval of Disposal

The Laboratory Director, in consultation with the patient's transplant physician, shall approve of product discard and method of disposal.

10.2.3 Method of Disposal

10.2.3.1 The method of disposal and decontamination shall meet current local rules and regulations for disposal of human tissues.

#### 10.2.4 Recording of Disposal

10.2.4.1 Records of disposal of products shall indicate the date and method of disposal.

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## **Section 11 RECORDS**

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### **11.1 GENERAL REQUIREMENTS**

#### 11.1.1 Systematic record keeping

11.1.1.1 Records shall be made during each step of the collection, processing, testing, cryopreservation and infusion or disposal of cellular product in such a way that all steps can be accurately traced.

11.1.1.2 Records shall be legible, permanent and indicate date (and times where appropriate) and the person responsible for each step.

11.1.1.3 Records of each step shall be as detailed as necessary for a clear understanding of each step by a person experienced in HSC and TC processing and transplantation, and shall be available for inspection by authorized individuals.

#### 11.1.2 Confidentiality

11.1.2.1 All records shall remain confidential and accessible only to the relevant staff who shall not divulge information to anyone else except to those who may be clinically involved with the use of the cellular product.

### **11.2 ELECTRONIC RECORDS**

#### 11.2.1 General definition

11.2.1.1 An electronic record is any record or document consisting of any combination of text or graphics or other data that is created, stored, modified, or transmitted in digital form by a computer.

#### 11.2.2 Authenticity and Confidentiality

11.2.2.1 If a computer record-keeping system is used, there shall be a system to ensure the authenticity, integrity and confidentiality of all records.

### 11.2.3 Security

11.2.3.1 There shall be a system whereby access is limited to authorized individuals.

### 11.2.4 True copies

11.2.4.1 There shall be an ability to generate true copies of the records in both paper and computer form suitable for inspection and review.

### 11.2.5 Integrity

11.2.5.1 Once the details of the record have been transcribed from the hard copy into the computer and the entry checked and validated, all subsequent alterations, including operator and date, shall be tracked and traceable.

### 11.2.6 Non-electronic Backup Procedures

11.2.6.1 The facility shall have an alternative system that ensures continuous operation in the event that computerized data are not available. The alternative system must be tested periodically.

## **11.3 RECORD MAINTENANCE**

Records shall be maintained, accessible and minimally include the following:

### 11.3.1 Records related to cell collection:

#### 11.3.1.1 Donor and recipient records:

- a) Donor selection, including medical history, physical examination and informed consent.
- b) Permanent and temporary deferrals for health reasons including reason (s) for deferral, and
- c) Donor adverse reactions, reports including results of all investigations and follow-up.

#### 11.3.1.2 Collection facility records:

- a) Records related to quality control, personnel training or competency, equipment and facility maintenance, facility management, or general facility issues.

### 11.3.2 Records related to cell processing and storage:

#### 11.3.2.1 Processing records:

- a) identity of any facility involved in the cell collection, processing, storage or transplantation

- b) Product processing, including lot numbers and expiry dates of reagents and disposables used, results and interpretation of all tests and re-test.
- c) Information on characterization of material and devices used in the manipulation of products including but not limited to antibodies, serum, cytokines, toxins, antibiotics, pharmacologic agents other chemicals or solid support. Records shall include the manufacturer's name and lot number of all reagent used.
- d) Records of laboratory personnel involved in labelling, processing, storage or distribution of products, including their name, signature, initials, and inclusive dates of employment.
- e) Documentation of donor's infectious disease testing results.
- f) Signature of the Laboratory Director authorizing the release of product in cases of where there is nonconforming product.

#### 11.3.2.2 Storage and infusion distribution records

- a) Distribution and disposition, as appropriate, of products.
- b) Visual inspection of liquid products during storage and immediately before infusion.
- c) Storage temperature, including initial temperature recorder charts.
- d) Reissue, including records of proper temperature maintenance, documentation of events requiring return, results of inspection upon return and actions taken to insure safety and viability prior to reissue.

#### 11.3.2.3 Compatibility and other test records:

- a) Results of all compatibility tests, including red cell compatibility testing of patient samples, antibody screening and identification.
- b) Results of other tests as stated in section 3.5.7 and 5.4 of this standard.

### 11.3.3 Records applicable to all facilities

11.3.3.1 Sterilizing of supplies and reagents prepared within the facility, including method, date, time interval and temperature.

11.3.3.2 Maintenance records of equipments

- a) Supplies and reagent, including name and manufacturer or supplier, lot numbers, date of receipt and expiration date
- b) Disposition or rejected supplies and reagents used in the collection, processing, testing, freezing and storage of products and
- c) Temperature charts and records of storage, including storage during transport.

11.3.3.3 Quality Control records:

- a) Calibration and standardization of equipment.
- b) Performance checks of equipment and reagents.
- c) Periodic check of aseptic technique.
- d) Periodic tests of capacity of shipping containers to maintain proper temperature in transit.
- e) Test results.
- f) Results of inspection and accreditation visits.
- g) Corrective action for non-conformance incidents.

**11.4 RECORDS IN CASE OF DIVIDED RESPONSIBILITY**

11.4.1 If more than one facility participate in any procedure or testing, a record of each contribution and outcome shall be kept.

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**Section 12**  
**QUALITY MANAGEMENT**

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**12.1 GENERAL**

- 12.1.1 In quality management of HSC collection, processing and storage, the principles of Good Manufacturing Practice are to be observed.
- 12.1.2 Where there are associated testing performed within the HSC laboratory, these tests shall be accredited.
- 12.1.3 The management of each facility shall establish and maintain Quality Management System (QMS).

**12.2 ORGANISATION**

- 12.2.1 There shall be a defined organizational plan for each service or facility.

**12.3 QUALITY MANAGEMENT SYSTEM**

12.3.1 Policies

- 12.3.1.1 There shall be coordinated policies and SOPs, protocols, staff training and quality improvement activities.
- 12.3.1.2 There shall be regular interactions between these facilities.
- 12.3.1.3 Each facility shall maintain a Quality Manual which document policies encompassing all quality system elements, including:
  - a) Description of facility and its scope of services
  - b) Quality policy
  - c) Staff education and training
  - d) Quality assurance
  - e) Document control
  - f) Records, maintenance and archiving
  - g) Accommodation and environment
  - h) Instruments, reagents and/or relevant consumables management

- i) Validation of examination procedures
- j) Safety
- k) Environmental aspects
- l) Research and development
- m) List of examination procedures
- n) Request protocols, primary sample, collection and handling of laboratory sample
- o) Validation results
- p) Quality control (including laboratory comparisons)
- q) Laboratory information system
- r) Reporting of results
- s) Remedial actions and handling of complaints
- t) Communications and other interactions with patients, health professionals, referral laboratories and suppliers
- u) Internal audits
- v) Ethics

### 12.3.2 Procedures

12.3.2.1 Each cell collection and cell processing facility shall maintain a detailed SOP.

12.3.2.2 The SOP shall include:

- a) Procedures for preparing, implementing and reviewing all procedures.
- b) A standardized format for procedures, including worksheets, reports and forms.
- c) A system of numbering and/or titling of individual procedures.

12.3.2.3 Procedures shall be sufficiently detailed and unambiguous to allow qualified laboratory staff to follow and complete the procedures successfully.

12.3.2.4 Each individual procedure requires:

- a) A clearly written description of the purpose.
- b) A clearly written description of equipment and supplies used.
- c) The objectives of the procedure, and acceptable end-points and the range of expected results.
- d) A reference section listing appropriate literature.

e) Documented approval of procedure and each procedural modification by the facility director or designee prior to implementation and annually thereafter, including the associated validation studies.

f) Examples of correctly completed worksheets, reports, labels and forms.

12.3.2.5 All procedures shall be the subject of a SOP which complies with these Standards.

12.3.2.6 Deviations from SOP shall be documented and approved by the facility director or designee.

12.3.2.7 Copies of the SOP shall be available in the immediate area to the facility staff at all times.

12.3.2.8 All personnel in the facility shall follow the standard operating procedures detailed in the SOP.

12.3.2.9 A permanent record should be maintained of all SOPs which have been revised/deleted.

## **12.4 DOCUMENT CONTROL**

12.4.1 All SOP shall be reviewed regularly, and a document version control system shall be implemented to ensure all documents made available to staff are current.

12.4.2 New and revised policies and procedures shall be read by the staff prior to implementation. This review and associated training shall be documented.

12.4.3 Archived procedures and their historical sequence shall be maintained for a period to be consistent with guidelines issued by the College of Pathology(COP)/Academy of Medicine/ Ministry of Health Malaysia guidelines and/or *Akta Arkib Negara*.

## **12.5 PROCESS IMPROVEMENT**

12.5.1 Non-Conformances

12.5.1.1 All non-conformances with policies and procedures shall be documented, and actions taken in response to those non-conformances shall also be documented.

12.5.1.2 A thorough investigation, including conclusions and follow-up, of any unexplained discrepancy or the failure of a product to meet any of its specifications shall be made and documented.

12.5.2 Regular internal audits shall be undertaken to ensure compliance with policies and procedures, and actions taken in response to noncompliance shall be documented.

12.5.3 A quality improvement process should be implemented that allows prospective identification of problems and preventative actions to be taken.

## **12.6 PERSONNEL AND TRAINING**

12.6.1 Personnel involved in cell collection or processing shall be appropriately qualified and trained and their competence shall be regularly assessed.

12.6.2 Training and competency assessments shall be according to documented protocols, and completion of these shall be recorded for each staff member.

## **12.7 EQUIPMENT**

12.7.1 Equipment used in the collection, processing, testing, freezing, storage, transportation, and infusion of products shall be maintained in a clean and orderly manner and located so as to facilitate cleaning and maintenance.

12.7.2 The equipment shall be inspected, standardised and calibrated on a regularly scheduled basis as described in the SOP.

12.7.3 Equipment employed in the sterilization of materials used in the collection or for disposal of contaminated cell products shall be designed, maintained and utilized to ensure the destruction of contaminating microorganisms.

## **12.8 SUPPLIES AND REAGENTS**

12.8.1 There shall be a program of quality management that is sufficiently comprehensive to ensure that reagents, equipment and procedures function as expected.

12.8.2 All supplies and reagents used in the collection, processing, testing, freezing, storage and infusion of products shall be stored in a safe, sanitary, and orderly manner.

12.8.3 All reagents used in the collection, processing, freezing, and infusion of products, including those manufactured by the processing facility, shall be sterile.

12.8.4 Whenever possible, reagents and supplies shall be approved for human use.

12.8.5 Supplies and reagents shall be used in a manner consistent with instructions provided by the manufacturer.

## **12.9 PROCESS CONTROL**

### 12.9.1 Laboratory Controls

12.9.1.1 Laboratory control procedures shall include:

- a) The establishment of scientifically sound appropriate assays, guidelines and test procedure for the evaluation of the products.
- b) Adequate provisions for monitoring the reliability, accuracy, precision and performance of laboratory test procedures and instruments.
- c) Adequate identification and handling of all test samples so that they are accurately related to the specific unit of the cell product being tested, or to its donor, or to the specific recipient, where applicable.

### 12.9.2 Validation and Qualification Requirements

12.9.2.1 Protocols shall be developed, implemented, and documented for the validation or qualification of significant components of facilities, processes, equipment, reagents, labels, containers, packaging materials, and computer systems.

12.9.2.2 Determination of which elements are validated or qualified shall be made by the responsible facility director in accordance with the quality management program.

12.9.2.3 Evaluation of validation studies will be reviewed with documentation of approval by the facility director, or designee, in accordance with the quality management program.

### 12.9.3 Errors, Accidents and Adverse reactions

12.9.3.1 Each cell collection/processing facility shall have a system for detecting, evaluating, documenting and reporting errors, accidents and suspected adverse reactions.

12.9.3.2 Corrective actions shall be documented, and reviewed subsequently by the facility director.

12.9.3.3 All suspected adverse reactions shall be evaluated promptly according to SOP, and reviewed by the facility director.

12.9.3.4 A written evaluation of reported adverse reactions shall be included as part of the cellular processing record and made available to the donor's or recipient's medical practitioner.

12.9.3.5 Notification, in accordance with all applicable laws and regulation of confirmed cases of transmissible disease in a recipient attributed to the donor cellular product(s) shall be reported in writing by the attending physician to the collection facility /processing facility in a timely manner.

#### 12.9.4 Safety Requirements

12.9.4.1 Each cell collection/processing facility and clinical transplantation program shall be operated in a manner to minimize risks to the health and safety of employees, donors, volunteers, and patients. Suitable environment and equipment shall be available to maintain safe operations.

12.9.4.2 There shall be procedures for biological, chemical, and radiation safety, as appropriate, and a system for monitoring training and compliance.

12.9.4.3 Cell collection must be handled at all times with precautions that recognize the potential for exposure to infectious agents.

12.9.4.4 Eating, drinking, smoking or the application of cosmetics or contact lenses shall not be permitted in work areas.

12.9.4.5 Refrigerators and freezers used for the storage of specimens, HSC or TC products, blood products, human tissues or reagents shall not be used for any other purpose.

12.9.4.6 Gloves and personal protective equipment and clothing shall be worn while handling human tissue specimens. Such gloves, protective equipment and clothing shall not be worn outside the work area.