دائـــــرة الـصـــحـــة
DEPARTMENT OF HEALTH

DOH STANDARD ON STEM CELL THERAPIES, PRODUCTS & REGENERATIVE MEDICINE

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Applies to:	All DOH-licensed healthcare professionals, providers, suppliers of stem cell products and laboratories engaged in the provision of stem cells, stem-cell based-products, and related cellular therapies, somatic-cell-therapy and tissue-engineered products and regenerative medicine products for the purpose of human use. This standard also applies to Insurers, TPAs and Medical Billing Offices.		
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This Standard should be read in conjunction with related UAE laws, DOH Standards, Policies and Manuals.
For more information, kindly visit: http://www.mohap.gov.ae and www.doh.gov.ae

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1. Purpose:
   1.1. The purpose of this standard is to set DOH's criteria for the provision of safe, effective, and of quality stem cells, stem-cell based-products, and related cellular therapies, somatic-cell-therapy and tissue-engineered products and regenerative medicine products for the purpose of human use in the Emirate of Abu Dhabi.

2. Scope:
   2.1. Applies to all DOH-licensed healthcare providers:
      2.1.1. Providing any form of stem cell and cellular therapies using stem cell derivatives and regenerative medicine, other than Hematopoietic transplant (including bone marrow transplants). Latter will be addressed in a separate document;
      2.1.2. Supplying stem cell products directly to clients; and
      2.1.3. Involved in the laboratory production of stem cell products.
   2.2. Applies to all healthcare professionals involved in the collection, production, and reinjection/ grafting/transplanting of stem cells and stem cell derivatives, especially allogeneic and autologous stem cells or stem cell derivatives;
   2.3. Applies to autologous and allogeneic stem cells including induced pluripotent cells and excludes the use of non-induced pluripotent stem cells. Acceptable sources of stem cells include the bone marrow, peripheral blood, adipose tissue, umbilical cord blood and placenta; and
   2.4. Excludes the use of such therapies and products for research purposes.

3. Definitions:
   3.1. **Embryonic Stem Cells**: the earliest stage of stem cell, growing and differentiating to eventually form every type of tissue in the human body. They are considered to be non-induced pluripotent and are derived from human embryos, who are aborted or left over from in vitro fertilization. They present a different DNA from the recipient of the cells. They can form tumor cells (teratomas)[1].
   3.2. **Good Laboratory Practice (GLP)**: a quality system concerned with the organizational process and the conditions, under which non-clinical health and environmental safety studies and research are planned, performed, monitored, recorded, archived and reported. [2]
   3.3. **Good Manufacturing Practice (GMP):** a system for ensuring that products are consistently produced and controlled to state-of-the-art quality standards appropriate to their intended use.
   3.4. **Homologous use:** is "the repair, reconstruction, replacement, or supplementation of a recipient's cells or tissues with a Human Cellular and Tissue-based product that performs

[1] Cell Surgical Network.
[2] OECD

the same basic function or functions in the new site as in the site from which it was extracted.

3.5. **Human cellular and tissue-based products (HCT/P):** HCT/Ps are articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient[3].

3.6. **Minimal manipulation:** Processing of cells and tissues that does not alter the original relevant characteristics and structure related to their original function or to their relevant biological characteristics. Regardless of the sources of the tissue sample e.g. peripheral blood, umbilical cord blood, placenta, amniotic fluid, bone marrow, adipose tissue, etc., the Stem Cells should not be isolated and or manipulated[4].

3.7. **Quality assurance:** a defined system. Including personnel, which is independent of study conduct and is, designed to assure test facility management of compliance[5].

3.8. **Recovery of HCT/P**: extraction of the tissue or cells from the same patient in the case of autologous cells or different donor in the case of allogeneic cells.

3.9. **Regenerative Medicine:** the process of stimulating the patient's tissue /cells or creating living, functional tissues to repair or replace tissue or organ function lost due to congenital defects, damage and/or aging. This field holds the promise of regenerating damaged tissues and organs in the body by stimulating previously irreparable organs to heal themselves[6].

3.10. **Responsible person:** Responsible person is defined as a person who is authorized to perform designated functions for which he or she is trained and qualified.

3.11. **Stem Cells:** are undifferentiated and unspecialized cells that have the capacity to regenerate (self-renewal) through cell division for long periods of time and which, under certain physiological or experimental conditions, can be induced to differentiate into specialized cell types (differentiation) with specific morphological characteristics and functions. Stem cells include the DNA but have not yet formed to become working cells. The main sources of stem cells are bone marrow, adipose tissue, and other sources such as the umbilical cord and organs.

3.11.1. **Adipose-derived Stem Cells:** stems cells that are isolated from human lipoaspirate tissue.

3.11.2. **Autologous Stem Cells:** stem cells that comes from a person's own body and so have the same DNA and express the same human leukocyte antigen (HLA) as the host and therefore cannot be rejected. Coming from a person's own body, they carry lower risks of transmission of infectious diseases.

[3] FDA Regulatory Considerations for Human Cells, Tissues, and Cellular and Tissue-Based Products: Minimal Manipulation and Homologous Use.
[4] Adapted from FDA Regulatory Considerations for Human Cells, Tissues and Cellular & Tissue-based Products, Guidance for Industry and Food & Drug Administration's Staff" Dec. 2017.
[5] OECD
[6] Cell Surgical Network

3.11.3. **Allogeneic Stem Cells:** are derived from genetically different individuals and hence have the donors' DNA and express the donors' HLA molecules raising the possibility of rejection of Graft versus host Disease (GVHD).

3.11.4. **Adult Mesenchymal Stem Cells:** are considered autologous and multipotent cells. Sources of Mesenchymal Stem cells are found all over the body with the bone marrow producing a continual flow of "Mesenchymal stem cells". Fat has an abundant source of Mesenchymal, and also hematopoietic cells. Adult stem cells come from bone, cartilage, muscle, nerve tissue, blood vessels, connective tissue, and fat[7].

3.11.5. **Multipotent:** same as mesenchymal stem cells. They are able to generate a number of cell typologies but not every typology.

3.11.6. **Pluripotent:** able to produce every typology of cells of the human organism but not able to induce a new organism.

3.11.7. **Induced Pluripotent:** originate from Adult cells that have been induced to become pluripotent stem cells as defined above.

3.12. **Stem Cell Therapy:** has the potential to repair, restore, replace, and regenerate cells, and could possibly be used to treat many medical conditions and diseases.

3.12.1. **Compassionate use:** as defined here is a treatment option where stem cell therapy/product in the investigational stage in the development stage is allowed by DOH to be used for patients who have a life-threatening conditions or serious conditions for which there are no satisfactory authorized therapies.

3.12.2. **Off Label use:** is the use of stem cell product in a manner different from that for which it initially received approval for as a drug by either using it to treat a different medical condition or by administrating it at a different dose or via a different route than originally approved.

3.13. **Stem Cell Products:** as defined here is a "cellular product derived from stem cells in vitro via differentiation or containing any quantity of stem cells"[8]. **Stem Cell Production:** the process of harvesting, culturing and manufacturing stem cells products/derivatives to produce a large enough quantity for therapeutic use.

3.13.1. **On-site production:** within the same facility where the HCT/P was recovered.

3.13.2. **Off-site production:** outside the facility where the HCT/P was recovered.

3.14. **Bio-vigilance:** "is the systematic monitoring of serious adverse reactions and incidents in the transplantation chain of substances of human origin, with the objective of making the application of tissues, cells and organs safer and more effective"[9].

3.15. **Infection Control:** are the policies, systems and procedures in place in healthcare facilities, including laboratories, designed to minimize the risk of spreading infections.

[7] Cell Surgical Network.

[8] Defining a stem cell product – working proposal and recommendations", Stem Cell Assays, Oct. 13, 2012

[9] TRIP-Hemo-en biovigilantie.

3.16. **Cellular Therapy:** the transplantation of human cells to replace or repair damaged tissue and/or cells. Many different types of cells may be used as part of a therapy or treatment for a variety of diseases and conditions, such as hematopoietic (blood-forming) stem cells (HSC), skeletal muscle stem cells, mesenchymal stem cells, lymphocytes, dendritic cells, and pancreatic islet cells[10].

3.17. **Regenerative Medicine:** the process of replacing or "regenerating" human cells, tissues or organs to restore or establish normal function. Regenerative Medicine refers to a group of biomedical approaches to clinical therapies that may involve the use of stem cells. Examples include cell therapies (the injection of stem cells or progenitor cells); immunomodulation therapy (regeneration by biologically active molecules administered alone or as secretions by infused cells); and tissue engineering (transplantation of laboratory grown organs and tissues)[11].

3.18. **Hematopoietic Stem Cell Transplantation:** the transplantation of multipotent hematopoietic stem cells, usually derived from bone marrow, peripheral blood, or umbilical cord blood. It may be autologous, allogeneic, or syngeneic (from an identical twin).

4. General Responsibility of Healthcare Facility/Provider:

4.1. To be licensed to provide stem cell and/or cellular therapies using stem cell derivatives;

4.2. To employ a multi-disciplinary team of healthcare professionals with the necessary qualifications and experience relevant to the particular cellular therapy provided;

4.3. To provide continuous training of staff;

4.4. To have an infection control policies and programs;

4.5. To have bio-vigilance policies and programs;

4.6. To keep a log of all patients who underwent cellular therapy including:

- 4.6.1. Patient name and demographics;
- 4.6.2. Laboratory site;
- 4.6.3. Source of cells (on-site; off-site);
- 4.6.4. Manipulation of cells/products/derivatives;
- 4.6.5. Recipient site: systemic or localized;
- 4.6.6. Therapeutic reasons;
- 4.6.7. Adverse events;
- 4.6.8. Infection;
- 4.6.9. Allergic reaction
- 4.6.10. Tumor formation
- 4.6.11. Growth of non-homologous tissue/abnormal tissue;
- 4.6.12. Expected therapeutic results: achieved/no results.
- 4.6.13. Follow up results at 6 months, 1 year, and 2 years;

[10] Adapted from AARB
[11] Adapted from AARB

4.7. Healthcare providers to make this information available to DOH representation if requested;

4.8. Provide patient education regarding the benefits and risks associated with the stem cell and/or cellular therapy using stem cell derivatives including but not limited to:

4.8.1. Infection;

4.8.2. Allergic reaction;

4.8.3. Tumor formation;

4.8.4. Growth of non-homologous tissue/abnormal tissue.

4.9. Obtain the consent of the patient before proceeding with the therapy. The consent form should provide the reason for the procedure, clear explanation of the risks and side effects associated with stem cell and other cellular therapy.

5. General Licensing Requirements:

5.1. Only licensed DOH healthcare facilities are eligible to provide Stem Cell Therapies and cellular therapies using stem cell derivatives;

5.2. Only licensed DOH healthcare care facilities can extract stem cells for use in stem cell therapies and regenerative medicine;

5.3. Only licensed DOH healthcare laboratories can manufacture stem cells within the Emirate of Abu Dhabi;

5.4. To be licensed to provide stem cell procedures and/or therapy and cellular therapy using stem cell derivatives, the healthcare provider must:

5.4.1. Show evidence of compliance with the requirements of a multi-disciplinary team with the relevant qualifications;

5.4.2. Indicate the type of cell therapy to be provided;

5.4.3. Show evidence that the therapy is a recognized approved therapy for the indication by international or regional drug approval bodies, or by international/regional medical associations/ societies;

5.4.4. If the above is not available, application for approval of the cellular therapy must be submitted to DOH-Abu Dhabi Health Research and Technology Committee (ADHRTC) prior to commencing with the licensing procedure. The application must include the protocols governing the production of stem cells and their therapeutic uses.

5.4.5. Show evidence of Good Laboratory Practice (GLP), Good Medical Practice (GMP), Good Tissue Practice (GTP) and Good Clinical Practice (GCP) if applicable.

5.5. In the case of compassionate use or off-label prescribing stem cell/cellular therapy, an application for approval of the intended use of stem cells/stem cell derivatives must be submitted to DOH-ADHRTC prior to initiation of the therapy. The application must include the protocols governing the production of stem cells and their therapeutic uses.

6. General Requirements - Healthcare Professionals:

In order to perform stem cell therapy, the healthcare professionals must:

6.1. Have a valid DOH license;

6.2. Practice within the specified scope of services of their facility, the job duties assigned to them by their employing facility and the privileges granted in accordance with the requirements of the DOH Clinical Privileging Framework Standard.

7. Specific Requirements - Stem Cell and Cellular Therapies in Abu Dhabi:

7.1. Stem cell therapies approved for use in Abu Dhabi are those therapies that are internationally approved/accepted as a standard treatment for their indications by recognized international drug regulatory bodies such as the FDA or equivalent or by international medical associations, societies or professional bodies. Therapies including bone marrow transplant and related transplant for the treatment of blood disorders and for the treatment of resulting complications will be addressed separately;

7.1.1. Inclusion & Exclusion:

7.1.1.1. Excludes bone marrow transplants which will be addressed separately;

7.1.1.2. Includes use of autologous cells for non-homologous functions; and

7.1.1.3. Includes use of allogeneic cells for homologous or non-homologous functions.

7.2. Patient eligibility-as determined by the treating physician for those therapies approved for use in Abu Dhabi Emirate as per Article 8.1 or are approved by DOH-Abu Dhabi Health Research Technology Committee (ADHRTC) for use in Abu Dhabi;

7.3. Therapies using Minimally Manipulated Autologous cells are generally internationally and DOH approved as cellular therapies, without the isolation of a specific stem cell;

7.3.1. Includes therapies where structural tissues are used for homologous functions such as use of Structural Stromal Vascular Fraction for the function of providing structural tissue cushioning and support;

7.3.2. Cannot be advertised as stem cell therapies;

7.3.3. Providers must be licensed to provide this type of structural tissue therapy.

7.4. Therapies using more than Minimally Manipulated Autologous or Allogeneic HCT/P:

7.4.1. Prior to applying for a license, the following criteria for regenerative medicine should be completed:

7.4.1.1. Supportive treatment for orthopedic related injuries or conditions;

7.4.1.2. Supportive treatment for other indications still under international study for approval;

7.4.1.3. “Compassionate use” treatment in the case of terminal patients with life threatening diseases;

7.4.1.4. Off-label use;

7.4.1.5. Investigational: To provide stem cell therapies that are still in the investigational stages, an application must be submitted to DOH-ADHRTC for approval.

7.5. Application to DOH-ADHRTC for approval of a specific cellular therapy as required under article 8.3.1 must include all the necessary production and treatment protocols.

8. Specific Requirements Collection and Production of stem cells:

8.1. Stem cells and stem cell derivatives must be harvested by appropriate health provider personnel depending of the sources of stem cells e.g. plastic surgeons for adipose tissue source, gynecologist for umbilical cord and placenta and specialist in aphaeresis for peripheral blood and manufactured in specific on-site or off-site laboratories accredited for production of stem cells;

8.2. Stem cells and stem cell derivatives must also be manufactured in specific on-site or off-site laboratories accredited for production of stem cells;

8.3. Recovery & Processing of Minimal Manipulated Autologous Tissue for Grafting:

8.3.1. Must be minimally manipulated;

8.3.2. Must be extracted and processed in minor operating rooms or clean procedure rooms;

8.3.3. Must be produced under sterile conditions and observe strict infection control measures preferably in closed systems;

8.3.4. to be extracted by plastic surgeons or other appropriately trained staff as per the source location of the cells within the body;

8.3.5. Therapy must be provided under sterile conditions by personnel trained in the collection of tissue for grafting procedures.

8.4. Recovery of Allogeneic HCT/P- off site:

8.4.1. Under sterile conditions;

8.4.2. Observing strict internal control methods/process and quality assurance methods;

8.4.3. Recovery (i.e. Extraction) by plastic surgeons or other medically trained staff as per the source location of the cells within the body;

8.4.4. Using internationally approved technology for stem cell recovery and processing.

8.5. Production of Autologous and Allogeneic HCT/P-Off-site:

If a facility is providing autologous or allogeneic HCT/P harvests off site, then, based on the location of the laboratory producing the cells, it has to be either:

8.5.1. Licensed by:

8.5.1.1. DOH if within Abu Dhabi Emirate; OR

8.5.1.2. The local regulator as a stem cell producing laboratory if elsewhere in the UAE; OR

8.5.2. Licensed and accredited by the respective national regulator and accreditation body if outside the United Arab Emirates;
8.5.3. UAE-based laboratory must be accredited to perform stem cell production and/or harvesting ;
8.5.4. Uses internationally approved stem cell production and recovery processes and technologies;
8.5.5. Must store the harvested stem cells in facilities approved for the storage of cellular products;
8.5.6. Shows evidence of the accreditation and the international approval.

8.6. Production of Autologous HCT/P-On site:
8.6.1. Under sterile conditions;
8.6.2. Observing strict infection control and quality assurance methods;
8.6.3. By trained staff;
8.6.4. Have a laboratory accredited for stem cell production and trained personnel using internationally approved production technology.

8.7. Shipping of HCT/P produced from off-site producers:
8.7.1. To follow the principles of Good Tissue Practice as elaborated in Appendix 2.
8.7.2. To follow the "Chain of command" system
8.7.3. Under strict conditions the transplantation including:
8.7.3.1. Specific container;
8.7.3.2. Specific preservation media within a maximum of 48 hours from collection to delivery.

9. Use of Pre-prepared Stem Cells Products:

9.1. Stem cells and/or stem cell products, including placental cells, to be used in cellular therapy in Abu Dhabi must have the necessary product approval by the any of the international regulation national agencies recognized by the UAE's Ministry of Health and Prevention;
9.2. The storage of stem cells, Cellular Bank, must comply with the standard regulations for the storage of cellular products.

10. Enforcement and Sanctions:

10.1. Healthcare Provider, Insurers, TPAs and Medical Billing Office must comply with the terms and requirements of this Standard.
10.2. DOH may impose sanctions in relation to any breach of requirements under this standard in accordance with the [DOH Policy on Inspections, Complaints, Appeals and Sanctions].

11. Appendix 1: Good Laboratory Practice[12]:

1. Infection Control

a. All equipment used in the procedure shall be sterile;
b. The Laboratory must comply with proper flow of samples and products;
c. Sterile techniques and aseptic conditions shall be used and maintained throughout procedure;
d. All staff must follow the rules and regulations of Good Laboratory Practice;
e. There must be a registry of every device or equipment used as part of compliance with requirements for bio-vigilance and infection control;
f. Proper biosafety cabinets are mandatory for processing biological samples;
g. Physicians and surgical technician shall wear hats, masks, and sterile gloves for procedure;
h. Hands must be washed between treatments;
i. Patients must be free of any systematic infection, dental infection, or periodontal disease;
j. Staff must be regularly tested for the presence of infectious diseases.

[12] Adapted from "OECD Series on Principles of Good Laboratory Practice and Compliance Monitoring http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=env/mc/chem(98)17&doclanguage=en

12. Appendix 2: Current Good Tissue Practice[13]:

A. General

a. Providers must follow FDA or European Union Current Good Tissue Practice (CGTP) requirements to prevent the introduction, transmission, or spread of communicable diseases by HCT/Ps (e.g., by ensuring that the HCT/Ps do not contain communicable disease agents, that they are not contaminated, and that they do not become contaminated during manufacturing).
b. Communicable diseases include, but are not limited to, those transmitted by viruses, bacteria, fungi, parasites, and transmissible spongiform encephalopathy agents.
c. CGTP requirements govern the methods used in, and the facilities and controls used for, the manufacture of HCT/Ps, including but not limited to all steps in recovery, donor screening, donor testing, processing, storage, labeling, packaging, and distribution. The CGTP provisions specifically governing determinations of donor eligibility, including donor screening and testing.
d. In the case of pre-prepared stem cell products, the manufacturer must provide the safety profile of the product including the data of the donors.

B. Core Current Good Tissue Practice (CGTP) Requirements

The following are core CGTP requirements:

i. Facility-Related Requirements

General

Any facility used in the manufacture of HCT/Ps must be of suitable size, construction, and location to prevent contamination of HCT/Ps with communicable disease agents and to ensure orderly handling of HCT/Ps without mix-ups. The facility must be maintained in a good state of repair and must be provided with levels of lighting, ventilation, plumbing, drainage, and access to sinks and toilets that are adequate to prevent the introduction, transmission, or spread of communicable disease.

Facility cleaning and sanitation

a. (1) Any facility used in the manufacture of HCT/Ps must be maintained in a clean, sanitary, and orderly manner, to prevent the introduction, transmission, or spread of communicable disease.
b. (2) Sewage, trash, and other refuse must be disposed of in a timely, safe, and sanitary manner.

ii. Environmental Control Requirements :

Environmental control:

Where environmental conditions could reasonably be expected to cause contamination or cross-contamination of HCT/Ps or equipment, or accidental exposure of HCT/Ps to communicable disease agents, they must be adequately controlled and the proper

[13] Adapted from: Food and Drug Administration—Title 21, Chapter 1, Subchapter L. Part 1271, Subpart D, Sec. 1271.150

conditions for operations must be provided. Where appropriate, the following control activities or systems must be provided:

a. Temperature and humidity controls;
b. Ventilation and air filtration (High Efficiency Particulate Air (HEPA) filtration);
c. Cleaning and disinfecting of rooms and equipment to ensure aseptic processing operations; and
d. Maintenance of equipment used to control conditions necessary for aseptic processing operations.

iii. Equipment-Related Requirements:

General

Equipment used in the manufacture of HCT/Ps must be of appropriate design for its use and must be suitably located and installed to facilitate operations, including cleaning and maintenance.

Any automated, mechanical, electronic, or other equipment used for inspection, measuring, or testing in accordance with this part must be capable of producing valid results.

Equipment must be cleaned, sanitized, and maintained, according to established schedules.

iv. Supplies and Reagents-Related Requirements:

Verification

Supplies and reagents should not be used until they have been verified to meet specifications designed to prevent circumstances that increase the risk of the introduction, transmission, or spread of communicable diseases. Verification may be accomplished by the establishment that uses the supply or reagent, or by the vendor of the supply or reagent.

Reagents

Reagents used in processing and preservation of HCT/Ps must be sterile, where appropriate.

v. Recovery-Related Requirements:

An establishment that extract/recovers HCT/Ps must recover each HCT/P in a way that does not cause contamination or cross-contamination during recovery, or otherwise increase the risk of the introduction, transmission, or spread of communicable disease through the use of the HCT/P.

vi. Processing & Process control-Related Requirements :

General:

An establishment that processes HCT/Ps, must process each HCT/P in a way that does not cause contamination or cross-contamination during processing, and that prevents the introduction, transmission, or spread of communicable disease through the use of the HCT/P.

Pooling:

Human cells or tissue from two or more donors must not be pooled (placed in physical contact or mixed in a single receptacle) during manufacturing.

In-process control and testing: In addition to the requirements with paragraph (a) of this section, each in-process HCT/P must be controlled until the required inspection and tests or other verification activities have been completed, or necessary approvals are received and documented. Sampling of in-process HCT/Ps must be representative of the material to be evaluated.

Dura mater:

- When there is a published validated process that reduces the risk of transmissible spongiform encephalopathy, this process must be used for dura mater (or an equivalent process that has been validated), unless following this process adversely affects the clinical utility of the dura mater.
- When using a published validated process, the process must be also verified in the establishment producing the stem cells.

vii. Labeling Control-Related Requirements:

General

Procedures to control the labeling of HCT/Ps must be designed, established and maintained to ensure proper HCT/P identification and to prevent mix-ups.

Verification

Verification" Procedures must include verification of label accuracy, legibility, and integrity.

viii. Storage-Related Requirements:

Storage areas and stock rooms must be controlled to prevent:

- Mix-ups, contamination, and cross-contamination of HCT/Ps, supplies, and reagents, and
- An HCT/P from being improperly made available for distribution.

Temperature: HCT/Ps must be stored at an appropriate temperature.

Expiration date: Where appropriate, each HCT/P must be assigned an expiration date based on the following factors:

- HCT/P type;
- Processing, including the method of preservation;
- Storage conditions; and
- Packaging.

Corrective action: Corrective action must be taken and documented whenever proper storage conditions are not met.

ix. Receipt, pre-distribution shipment, and distribution-Related Requirements:

Receipt:

Each incoming HCT/P must be evaluated for the presence and significance of microorganisms and inspected for damage and contamination. There must be pre-

established criteria on which basis decisions are made to accept, reject, or place in quarantine each incoming HCT/P to prevent communicable disease transmission.

Pre-distribution shipment:
For intra or inter-facility shipping of HCT/P (e.g., procurer to processor) and the HCT/P is not available for distribution as described in paragraph (c) of this section but is to be shipped either intra-facility or inter-facility, then it must be first determined and documented whether the pre-established criteria designed to prevent communicable disease transmission have been met, and HCT/P in quarantine must be the one shipped.
Availability for distribution:

- Before making an HCT/P available for distribution, its manufacturing and tracking records must be reviewed to verify that the release criteria have been met. Availability of the HCT/P for distribution based on the results of the verification must be documented and dated.
- An HCT/P must not be available for distribution that is in quarantine, is contaminated, is recovered from a donor who has been determined to be ineligible or for whom a donor-eligibility determination has not been completed (except as approved by DOH), or that otherwise does not meet the release criteria designed to prevent communicable disease transmission.
- Any HCT/P manufactured under a departure from a procedure relevant to preventing risks of communicable disease transmission should not be made allowed under any circumstances.

Packaging and shipping:
Packaging and shipping containers must be designed and constructed to protect the HCT/P from contamination and loss of cell viability.
The facility must establish the appropriate shipping conditions to be maintained during transit for each type of HCT/P.

x. Donor eligibility determinations, donor screening, and donor testing-Related Requirements:

Determination of the eligibility of a donor must be based on results of donor screening and donor testing in accordance. A responsible person must determine and document the eligibility of a cell or tissue donor.

Eligible donor: A donor is eligible if:

- Donor screening in accordance indicates that the donor:
  i. Is free from risk factors for, and has no clinical evidence of infection due to relevant communicable disease agents and diseases; and
- The results of donor testing for relevant communicable disease agents are negative or nonreactive.

Screening of a donor:

- All donors. The establishment that performs donor screening must screen a donor of cells or tissue by reviewing the donor's relevant medical records for:

i. Risk factors for, and clinical evidence of, relevant communicable disease agents and diseases, including:
   1. Human immunodeficiency virus;
   2. Hepatitis B virus;
   3. Hepatitis C virus;
   4. Human transmissible spongiform encephalopathy, including Creutzfeldt-Jakob disease;
   5. Treponema pallidum ;

Donors of viable, leukocyte-rich cells or tissue:
In addition to the relevant communicable disease agents and diseases for which screening is required under paragraph (a) of this section, the relevant medical records of a donor of viable, leukocyte-rich cells or tissue must be reviewed for risk factors for and clinical evidence of relevant cell-associated communicable disease agents and diseases, including Human T-lymphotropic virus.

Ineligible donors.
A donor is ineligible if assessed to have either of the following:

- A risk factor for or clinical evidence of any of the relevant communicable disease agents or diseases for which screening is required under paragraphs (a)(1), (b), or (c) of this section;

Abbreviated procedure for repeat donors

- If a complete donor screening procedure was performed on a living donor within the previous 6 months, an abbreviated donor screening procedure on repeat donations must be performed.

- The abbreviated procedure must determine and document any changes in the donor's medical history since the previous donation that would make the donor ineligible, including relevant social behavior.

Donor Testing General Requirements:

- Specimen from the donors must be tested for evidence of infection to any of the communicable disease agents identified above.

- For the communicable diseases agents listed above. In the case of a donor 1 month of age or younger, a specimen from the birth mother instead of a specimen from the donor should be tested.
  i. Timing of specimen collection. The donor specimen for testing must be collected at the time of recovery of cells or tissue from the donor; or up to 7 days before or after recovery, except:
  ii. (1) For donors of peripheral blood stem/progenitor cells, bone marrow (if not excepted under 1271.3(d)(4)), donor specimen for testing may be collected up to 30 days before recovery;

- Tests.
  i. Appropriate tests kits could be either ones licensed for and approved for donor testing.
  ii. In certain conditions where these are not available, licensed, approved, or cleared tests labeled for the detection of those organisms in an asymptomatic, low-prevalence population may be used. This is especially the case for testing for Chlamydia trachomatis and for Neisseria gonorrhea.

- Ineligible donors. The following donors should be considered ineligible:
  i. A donor whose specimen tests is reactive on a screening test for a communicable disease agent except for a donor whose specimen tests reactive on a non-treponemal screening test for syphilis and negative on a specific treponemal confirmatory test;
     1. A donor in whom plasma dilution is sufficient to affect the results of communicable disease testing is suspected, unless:
        - The test specimen was taken from the donor before transfusion or infusion and up to 7 days before recovery of cells or tissue; or
        - The plasma dilution sufficient to affect the results of communicable disease testing has not occurred as indicated by the algorithm used to evaluate volumes in the 48 hours before specimen collection. .
  ii. Clinical situations in which the plasma dilution is sufficient enough to be suspected of affecting the results of communicable disease testing include but are not limited to the following:
     1. Blood loss is known or suspected in a donor over 12 years of age, and the donor has received a transfusion or infusion of any of the following, alone or in combination:
        - More than 2,000 milliliters (mL) of blood (e.g., whole blood, red blood cells) or colloids within 48 hours before death or specimen collection, whichever occurred earlier, or
        - More than 2,000 mL of crystalloids within 1 hour before death or specimen collection, whichever occurred earlier.
     2. Regardless of the presence or absence of blood loss, the donor is 12 years of age or younger and has received a transfusion or infusion of any amount of any of the following, alone or in combination:
        - Blood (e.g., whole blood, red blood cells) or colloids within 48 hours before death or specimen collection, whichever occurred earlier, or
        - Crystalloids within 1 hour before death or specimen collection, whichever occurred earlier.
     3. Required donor tests for different types of cells and tissues:

- All donors. A specimen from the donor of cells or tissue, whether viable or nonviable, must be tested for evidence of infection due to relevant communicable disease agents, including:
  i. Human immunodeficiency virus, type 1;
  ii. Human immunodeficiency virus, type 2;
  iii. Hepatitis B virus;
  iv. Hepatitis C virus; and
  v. Treponema pallidum.
- Donors of viable, leukocyte-rich cells or tissue. In addition to the relevant communicable disease agents for which testing is required under paragraph (a) of this section,
  i. A specimen from the donor of viable, leukocyte-rich cells or tissue must be tested to adequately and appropriately reduce the risk of transmission of relevant cell-associated communicable diseases, including:
  1. Human T-lymphotropic virus, type I; and
  2. Human T-lymphotropic virus, type II.
  i. A specimen from the donor of viable, leukocyte-rich cells or tissue must be tested for evidence of infection due to cytomegalovirus (CMV), to adequately and appropriately reduce the risk of transmission. Standard Operating Procedure should be established and maintained to govern the release of an HCT/P from a donor whose specimen tests reactive for CMV.
- Dura mater. For donors of dura mater, an adequate assessment designed to detect evidence of transmissible spongiform encephalopathy must be performed.

xi. Compliance with applicable requirements:

1. Manufacturing arrangements:
   - Establishments that engage in some and not all of the operations listed above need only comply with those requirements applicable to the operations that they perform.
   - If an establishment seeks to engage another establishment (e.g., a laboratory to perform communicable disease testing, or an irradiation facility to perform terminal sterilization), whether under a contract, agreement, or other arrangement, to perform any step in the manufacturing process for the requesting establishment, then the engaged establishment is responsible for complying with the requirements applicable to that manufacturing step.
   - Before entering into an engagement arrangement (through a contract, agreement, or other arrangement) with another establishment to perform

any step in manufacture for the requesting establishment, the requesting establishment must ensure that the engaged establishment complies with applicable CGTP requirements.

If during the course of engagement period, the requesting establishment becomes aware of information suggesting that the engaged establishment may no longer be in compliance with such requirements, the former must take reasonable steps to ensure that the latter complies with those requirements. If the requesting establishment determines that the engaged establishment in not in compliance with those requirements then it should terminate the engagement arrangement.

2. Establishments that determine that an HCT/P meets all release criteria and makes the HCT/P available for distribution are responsible for reviewing manufacturing and tracking records to determine that the HCT/P has been manufactured and tracked in compliance with the requirements. This holds even if they are not the actual distributors.

3. When a requirement is qualified by "where appropriate," it is deemed to be "appropriate" unless justification otherwise can be documented. A requirement is "appropriate" if no implementation of the requirement could reasonably be expected to result in the HCT/P not meeting its specified requirements related to prevention of introduction, transmission, or spread of communicable diseases, or in the establishment's inability to carry out any necessary corrective action.