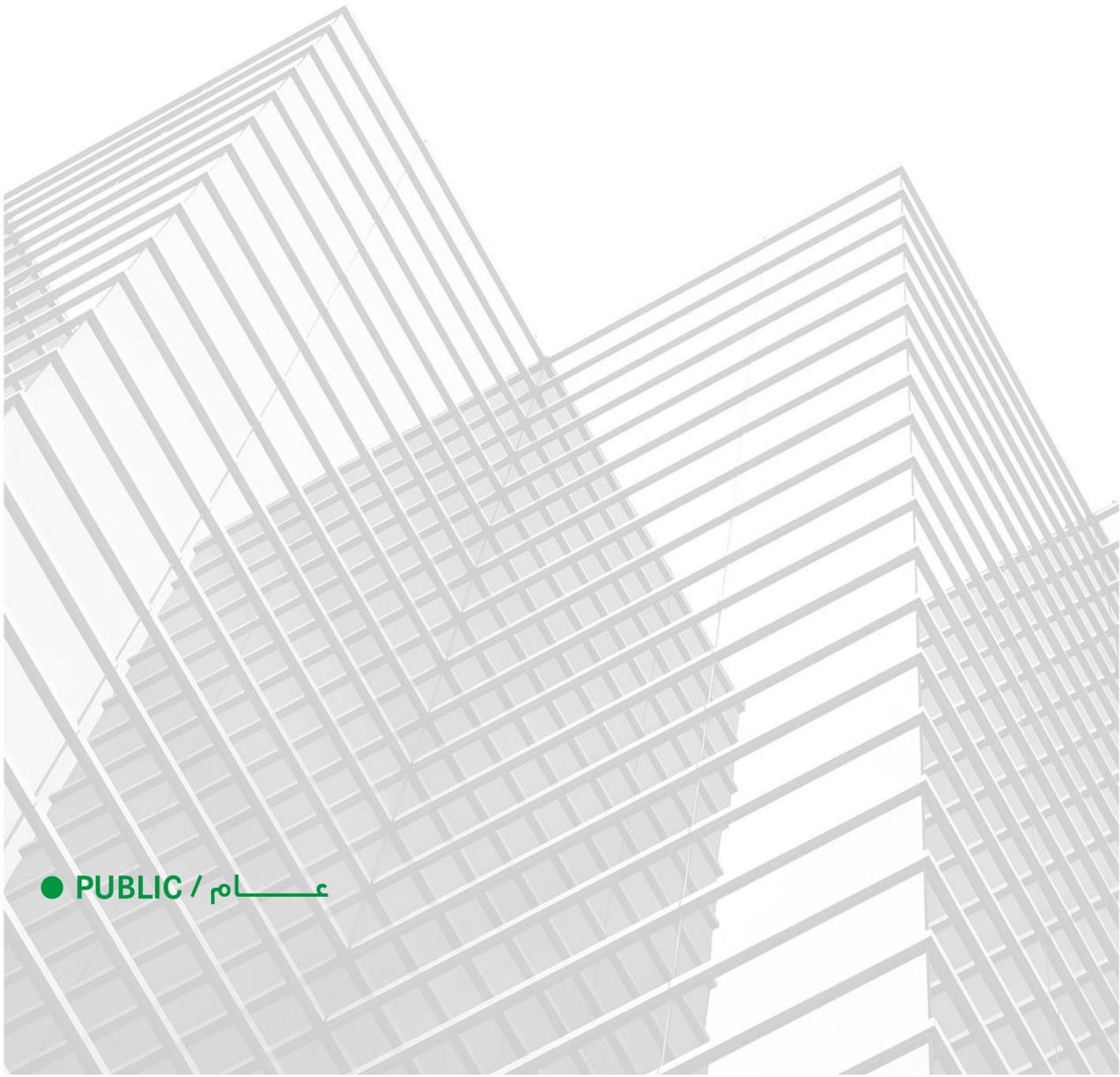
دائـــــرة الـصـــحـــة
DEPARTMENT OF HEALTH

Standard for Stem Cell Therapies Products and Regenerative Medicine



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Applies To:	- DOH-licensed healthcare professionals, providers, suppliers of stem cell products and laboratories engaged in the provision of and manufacturing 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. - Insurers, TPAs and Medical Billing Offices.		
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1.Standard Purpose and Scope

1.1. Purpose

The purpose of this standard is to set following DOH's minimum requirements for the provision of stem cells harvesting and the provision of safe, effective, and quality stem cell-, cell-based therapy and tissue-based products, cellular therapies, somatic-cell-therapy and tissue-engineered products and regenerative medicine products and interventions for the purpose of human use in the Emirate of Abu Dhabi.

1.2. Scope

1.2.1. The standard covers All DOH-licensed healthcare providers:

- 1.2.1.1. Providing any form of stem cell-, cell-, and tissue-based therapies, other than hematopoietic transplant.
- 1.2.1.2. Using human stem cell derivatives for regenerative medicine.
- 1.2.1.3. Supplying stem cell products directly to clients.
- 1.2.1.4. Involved in the harvesting of stem cells and the production of stem cell-, cell-, and tissue-based products, therapies and interventions.

1.2.2. This standard does not apply to:

- 1.2.2.1. The use of stem cell-based therapies and products only for research purposes.

The application of hematopoietic stem cell- based therapies and products, since it is addressed in DOH Standard for Center of Excellence in Hematopoietic Stem Cell Transplantation (HSCT) Services for Adults and paediatrics.

2. Definitions and Abbreviations

No.	Term / Abbreviation	Definition
2.1	**ADHRTC**	**A**bu **D**habi **H**ealth **R**esearch and **T**echnology **C**ommittee is an oversight committee that has been established by DOH to oversee and support critical human subject research carried out by various healthcare providers from public or private healthcare providers, and to advise on and promote health research in the Emirate of Abu Dhabi.
2.2	**Acceptable limits**	Set of criteria (numerical limits, ranges, or other criteria for tests) to which a drug substance or drug product should conform to be considered acceptable for its intended use.
2.3	**Accreditation**	System with a formal process for evaluating and recognizing the quality of an institution's services and competence. It is conducted by an official authorized organization.
2.4	**Adult Mesenchymal Stem Cells**	These 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 cells, and also hematopoietic cells. Adult stem cells come from bone, cartilage, muscle, nerve tissue, blood vessels, connective tissue, and fat.
2.5	**Allogeneic**	Stem cells derived from different individuals other than the donor, that will be used for medical or research purposes, such as tissue repair or cell-based therapies.
2.6	**Autologous**	Stem cells derived from the same individual that will be used for medical or research purposes, such as tissue repair or cell-based therapies. It carries the same DNA and human leukocyte antigen (HLA) as the human subject.

2.7	**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.
2.8	**Biobank**	Large collection of human biological materials (biospecimens) held for health and medical research purposes. Biobanks contain relevant personal and health information (which may include health records, chronic illnesses, history of recent infections, family history, lifestyle, and genetic information).
2.9	**Biovigilance**	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
2.10	**CAP-ISO 15189**	CAP-ISO 15189 is a quality management program that provides accreditation to ISO 15189, an international quality standard for medical laboratories.
2.11	**Cell Therapy**	A therapy that has the potential to repair, restore, replace, and regenerate cells, and could possibly be used to treat many medical conditions and diseases.
2.12	**Clinical Trial**	Research study performed in humans that aims to evaluate a medical, surgical, or behavioural intervention.
2.13	**Compassionate use**	Treatment option that allows the use of an unauthorised medicine alone or in combination with other available therapeutics. Under strict conditions, products in development can be made available to groups of patients who have a disease with no satisfactory authorised therapies and who cannot enter clinical trials.
2.14	**Current Good Tissue Practice (CGTP)**	Set of quality standards and guidelines that govern the collection, processing, storage, and distribution of human tissues for medical use. CGTP ensures that tissues are safe, effective, and traceable, and that they meet regulatory requirements.
2.15	**Good Laboratory Practice (GLP)**	Set of rules and criteria for a quality system concerned with the organizational process and the conditions under which non-clinical health and environmental safety studies are performed.
2.16	**Good Manufacturing Practice (GMP)**	System that guarantees controlled manufacturing of products in accordance with quality standards.
2.17	**Healthcare facility/provider**	Entity licensed by the Department of Health of Abu Dhabi that is involved in the direct delivery of healthcare and/or supportive healthcare services, or in the financing of health such as health insurer and health insurance facilitator, healthcare claims management entity, payer, Third Party Administrator (TPA's), hospital, medical clinic and medical center, telemedicine provider, laboratory and diagnostic center, and pharmacy, amongst others.
2.18	**Hematopoietic Stem Cell Transplantation**	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).
2.19	**Homologous use**	The repair, reconstruction, replacement, or supplementation of a recipient's cells or tissues with a Human Cellular and Tissue-based product that performs the same basic function or functions in the new site as in the site from which it was extracted.
2.20	**Human cellular and tissue-based products (HCT/Ps)**	Articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient.
2..21	**Human Embryonic Stem Cell (hESC)**	Pluripotent cell capable of differentiating into all somatic cell types of a human being. It is found in the inner cell mass of the human blastocyst during days 4 to 7 after fertilization.

2.22	**Research Ethics Committee (REC)**	Independent body formally designated to review, approve, and monitor biomedical and behavioral research involving humans with the aim to protect the rights and welfare of the subjects.
2.23	**Induced pluripotent stem cells (iPSCs)**	Differentiated cells that have been reprogrammed to a pluripotent state, meaning they can differentiate into any cell type in the body. They are created by introducing specific genes into the adult cells, essentially "turning back the clock" to a more embryonic-like state.
2.24	**Infection Control**	Policies, systems and procedures in place in healthcare facilities, including laboratories, designed to minimize the risk of spreading infections.
2.25	**Informed consent**	Virtual or hand-signed document that informs subjects about what they can expect from participating in a research study.
2.26	**Institutional Stem Cell Research Committee (ISCRC)**	Specialized and multidisciplinary oversight body established within the facility to review all aspects of stem cell research and applications performed.
2.27	**International Conference on Harmonisation Good Clinical Practice (ICH-GCP)**	International ethical and scientific quality standards for designing, recording and reporting trials that involve the participation of human subjects.
2.28	**Joint Commission International (JCI)**	JCI accreditation and certification identifies, measures, and shares best practices in quality and patient safety with the world to provide innovative solutions to help health care organizations across all settings improve performance and outcomes.
2.29	**License**	A permission given by the competent authority to practice a profession, activity or provide a healthcare service.
2.30	**Mesenchymal stromal cells (MSC)**	Also known as mesenchymal stem cells. Type of adult stem cell present in various tissues of the body, such as the bone marrow, fat, and umbilical cord tissue. They can differentiate into bone, fat, and cartilage cells, among others.
2. 31	**Minimal manipulation**	Processing level of cells and tissues that does not alter the original relevant characteristics and structure related to their original function or their relevant biological characteristics. For example: isolation, separation, washing, culturing without biological and chemical treatment, among others.
2.32	**Mitochondrial Replacement Techniques (MRT)**	Novel procedures designed to prevent the maternal transmission of mitochondrial DNA (mtDNA) diseases, which are rare, severely debilitating, progressive, and often fatal in infancy or childhood.
2.33	**Non-homologous use**	Intended therapeutic use of cells outside their native physiological context, such as the transplantation of hematopoietic cells or mesenchymal stromal cells into the heart or brain
2.34	**Off-label use**	Use of approved pharmaceutical drugs for an unapproved indication or in an unapproved age group, dosage, or route of administration.
2.35	**Pluripotent**	Able to produce every typology of cells of the human organism but not able to induce a new organism.
2.36	**Protected Health Information**	Past, present or future physical or mental health or condition of a patient; the provision of health care to a patient; or the past, present or future payment for the provision of health care to a patient.
2.37	**Purity**	Relative freedom from extraneous material in the finished product, whether or not harmful to the recipient or deleterious to the product.
2.38	**Quality assurance**	All the planned and systematic activities implemented within the quality system that can be demonstrated to provide confidence that a product or service will fulfill requirements for quality."
2.39	**Quality Management System (QMS)**	A formalized system that documents processes, procedures, and responsibilities for achieving quality policies and objectives. A QMS helps coordinate and direct an organization’s activities to meet

		customer and regulatory requirements and improve its effectiveness and efficiency on a continuous basis.
2.40	**Regenerative medicine**	Branch of medicine that focuses on the development of new therapies to repair, replace or regenerate damaged or diseased cells, tissues or organs and involves the use of stem cells, tissue engineering and other advanced technologies to promote healing and to restore normal function.
2.41	**Sensitive data**	Confidential information, including personal information whose processing could create significant risks to affected party. The following, but not limited to, are considered sensitive data: racial or ethnic origin, political opinions, religious or philosophical beliefs, trade union membership, genetic data, biometric data, data concerning health, technical configurations and architectures, classified government decisions/communications.
2.42	**Somatic Cell**	Any cell type of an organism other than reproductive cells.
2.43	**Stem Cell**	Undifferentiated and unspecialized cell that has 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.
2.44	**Stem Cell Product**	Cellular product derived from stem cells *in vitro* via differentiation or containing any quantity of stem cells.
2.45	**Stem Cell Production**	The process of harvesting, culturing and manufacturing stem cells products/derivatives to produce a large enough quantity for therapeutic use.
2.46	**Substantial manipulation**	Processing level of cells and tissues that alters the main original characteristics and/or functions of the cell. The processes include isolation, purification, genetic manipulation, tissue culture, among others.
2.47	**Tumorigenicity**	Measurement of the tumor-producing/cancer cell-producing potency of an agent.
2.48	**Viability**	Measure of the proportion of live, healthy cells within a population.

3.Standard Requirements and Specifications

3.1 Stem Cell Handling/manipulation Licensure

To be licensed to provide stem cell- and cell-related procedures and/or therapies, the healthcare provider must:

3.1.1 **Healthcare Providers**

3.1.1.1 Be licensed by DOH as a healthcare facility. Only healthcare facilities licensed by the DOH are eligible to provide stem cell-, cell-, and tissue-based therapies.

3.1.1.2 Have an Institutional Stem Cell Research Committee (ISCRC) or local Research Ethics Committee (REC) capable of providing a specialized internal oversight mechanism related to the therapy and/or product. The local ISCRC/REC will be the sole responsible body to seek ADHRTC approval.

3.1.1.3 The therapy is approved by reputable stem cells organizations, and HCF has international accreditation/registration in one of the known international research entities for stem cells.

3.1.1.4 Ensure the procurement (collection, biobank access, or import) of the stem cells and derivatives is performed by DOH licensed facilities or GMP certified facilities.

3.1.1.5 Ensure that the handling of stem cells and derivatives is carried out by DOH-licensed laboratories for manufacturing processes, which can be either on-site or off-site.

3.1.1.6 Comply with the existing regulations and guidelines to ensure that the product is safe, pure, and potent meeting CGTP, GMP and GCP requirements.

3.1.1.7 Obtain approval from ADHRTC and ISCRC or local Research Ethics Committee (REC) prior to the application of stem cell-, cell-, and tissue-based therapies.

3.1.2 **Healthcare professionals**

3.1.2.1 Provide evidence that a qualified multidisciplinary team comprise of staff with expertise in the therapy or product to be provided and ensure all staff have a clean history in stem cells therapy and have never been reported anywhere for ethical misuse of stem cells.

3.1.2.2 Show evidence that the personnel are licensed by DOH.

3.1.2.3 Ensure the staff performs their duties and activities under the DOH Standard for Clinical Privileging of Healthcare Workforce and Clinical Services.

3.1.2.4 Ensure healthcare professionals are certified depending on their roles (e.g.: ICH-GCP for clinicians, GLP and GTP for laboratory staff, among others).

3.1.3 **Therapies**

3.1.3.1 Indicate the type of therapy to be provided (**Figure 1**).

3.1.3.1.1 To correctly classify the therapy, it is recommended to refer to DOH Guidelines for Research and Clinical Translation in Stem Cells and receive counselling from the ISCRC Or local Research Ethics Committee (REC).

3.1.3.2 Obtain REC/ISCRC and ADHRTC authorization per therapy and depending on its type (**Figure 1**).

3.1.3.3 Provide a detailed protocol of the therapy/product application, which must be carefully designed with well-defined primary and secondary outcomes.

3.1.3.4 Provide evidence that the therapy is a recognized approved therapy for the indication by international or regional drug approval bodies (e.g.: FDA, EMA), or by international/regional medical associations/societies. If this is not possible:

3.1.3.4.1 An application for approval from ADHRTC is required prior to the licensing procedure. Protocols of the procurement, production, associated risks, and therapeutic uses must be included and detailed in the application.

3.1.3.4.2 Nonclinical evidence on the proof-of-principle and safety in a relevant animal model before the administration to humans must be provided for ADHRTC's approval.

3.1.3.4.3 A risk-based approach can be applied while giving regulatory approvals as long as it does not compromise patient's safety, such as conditional marketing authorization.

3.1.3.5 Minimally manipulated and homologous use therapies must be referred to as "Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps)" instead of "stem cell therapies".

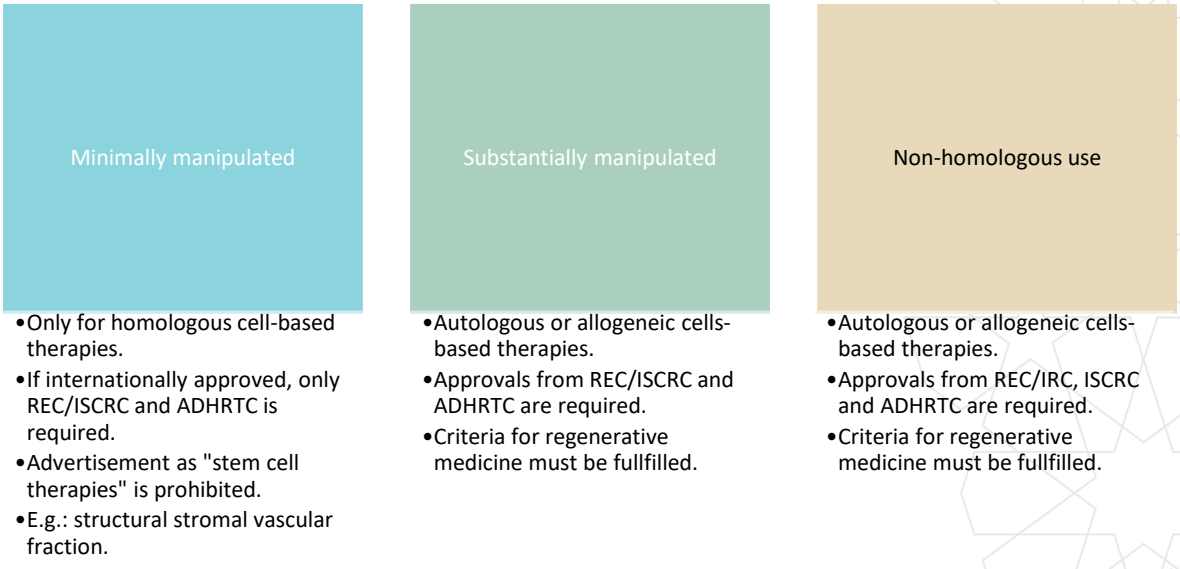

Figure 1. Regulatory requirements for the use of stem cell-, cell-, and tissue-based therapies.

3.1.3.6 For more than minimally manipulated interventions (substantially manipulated and for non-homologous use), the healthcare facility must comply with one criterion for regenerative medicine listed below:

3.1.3.6.1 Supportive treatment for orthopedic related injuries or conditions.

3.1.3.6.2 Supportive treatment for other indications (e.g.: neurological disorders, diabetes, autoimmune diseases, cardiovascular diseases, tissue regeneration, among others) still under international study for approval.

3.1.3.6.3 Compassionate use treatment in the case of terminal patients with life threatening diseases.

3.1.3.6.4 Off-label use.

3.1.3.6.5 Investigational: to provide therapies that are still in the investigational stages, an application must be submitted to ADHRTC for approval.

3.1.3.7 Develop inclusion/exclusion criteria for donor eligibility depending on the therapy/product to be provided.

3.1.3.8 Determine procedures for the follow-up period, which must be for at least two years.

3.1.3.8.1 It could be longer depending on the type and source of cells used, the intended clinical application, and age and gender of the recipient.

3.1.4 **Patients**

3.1.4.1 Patients receiving treatment with unproven stem cell-based, cell-, and tissue-based interventions under the purview of clinical trials must not be charged for any procedure(s) related to the trial including healthcare facility stay and laboratory investigations.

3.1.4.2 The informed consent must be robust and understandable for patients. It must include information of associated benefits and risks related to the therapy/product, such as the risk of infections, allergic reactions, tumor formation and growth of non-homologous tissue/abnormal tissue associated, among others.

3.1.4.3 Measures to enhance the treatment consent obtention must be considered, some of these include but are not limited to:

3.1.4.3.1 The person who conducts the informed consent dialogue must not have vested interests.

3.1.4.3.2 Space and time to answer questions must be provided.

3.1.4.3.3 Counselling services must be made available upon request.

3.1.4.3.4 Explain the current status on the application of stem cells in the given condition, experimental nature of the proposed clinical study and its possible short and long-term risks and benefits.

3.1.4.3.5 Provide additional educational materials.

3.1.4.3.6 Test the consent comprehension regarding the risks and benefit associated to the intervention before accepting the consent.

3.1.4.3.7 It is recommended to follow DOH Guidelines for Research and Clinical Translation in Stem Cells.

3.2 Stem Cell Procurement

3.2.1 **Collection and recovery**

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

3.2.1.2 Informed consent must be obtained prior to the collection of human biological material, which can be obtained from an autologous or allogeneic source. This donor consent must be different from the consent obtained for treatment.

3.2.1.2.1 The informed consent must be robust and understandable for patients. It must include the risks associated with the procurement procedures. It is strongly recommended to follow DOH Guidelines for Research and Clinical Translation in Stem Cells.

3.2.1.2.2 Measures to prevent the exploitation and commoditization of donors must be taken.

3.2.1.3 Harvesting must be conducted by a specialist with expertise on the source of the stem cell, such as the listed in **Table 2**. The harvesting for other sources and/or with other specialists, not shown in **Table 2,** can also be performed as long as safety and expertise are addressed and only after approvals of ADHRTC and REC/ISCRC.

3.2.1.4 Policies must be developed to avoid misuse of human biological material.

3.2.1.5 Standard Operating Procedures (SOPs) must be developed for the collection of human biological materials, considering biosafety measures, GLP and ICH-GCP.

Table 2.- Healthcare professionals authorized for collection stem cells based on the biological material source.

Healthcare professional	Source
Plastic surgeon	Adipose tissue
Gynaecologist	Umbilical cord, placenta
Aphaeresis specialist	Peripheral blood
Neurosurgeon	Neural samples
Haematologist	Bone marrow
Surgeon	Special samples

3.2.1.6 The collection and recovery must be performed under sterile conditions in minor operation rooms or clean procedure rooms.

3.2.1.7 Strict infection control measures and quality assurance methods must be considered, to avoid contamination during the procedure.

3.2.1.8 Only internationally approved technology for stem cell isolation must be used.

3.2.1.9 If the procedure involves minimally manipulated autologous tissue for grafting, the therapy must occur in the same sterile conditions by personnel trained in the harvesting of the tissue.

3.2.1.10 Screening of communicable diseases must be performed.

3.2.1.11 Additional tests must be performed to ensure the quality and safety of human biological materials. (e.g.: genetic tests, complete hemogram, travel history review, among others).

3.2.2 **Biobank**

3.2.2.1 HCT/Ps, stem cells and/or stem cell-based products to be used in cellular therapy in Abu Dhabi must have the necessary product approval by any of the international regulations or national agencies recognized by the UAE's Ministry of Health and Prevention.

3.2.2.2 Cells and tissues obtained from biobanks must comply with the requirements of DOH Standard on Biobanking for Stem Cells.

3.2.2.3 The safety profile of the donor of the biological materials must be provided by the biobank.

3.2.3 **Import**

3.2.3.1 Human embryonic stem cell lines and somatic stem cell lines are exempt from approval of ADHRTC if they have been previously approved and imported to Abu Dhabi.

3.2.3.2 ADHRTC approval is required for cell lines that have not been previously imported to Abu Dhabi.

3.2.3.3 The facility must review and ensure that the cell line has been adequately processed, manufactured, and procured with ethical principles compatible with laws and regulation of Abu Dhabi and obtained with a fully informed and free donor consent.

3.2.3.4 Healthcare facilities are responsible for importing biological materials in accordance with Abu Dhabi regulations, including documentation, packaging and declarations.

3.3 Processing and Handling of Stem Cells and derivatives

3.3.1 General requirements

Only laboratories licensed by DOH can process and handle stem cells and derivatives for the purpose of human use within Abu Dhabi. The laboratory may be located on-site within the healthcare facility that provides stem cell-based therapies or off-site externally. Regardless of its location, it must meet the following requirements:

3.3.1.1 Attain accreditation by a national or international recognized body, such as CAP-ISO 15189, JCI, among others.
3.3.1.2 Comply with this standard and DOH Clinical Laboratory Standards to provide quality, accurate, and reliable laboratory tests, products, and services.
3.3.1.3 Comply with related DOH guidelines, standards and regulations. **(Refer to 3.2**)
3.3.1.4 Demonstrate evidence of Good Laboratory Practice (GLP), Good Clinical Practice (GCP), Good Manufacturing Practice (GMP), Good Storage Practice (GSP), and Current Good Tissue Practice (CGTP) as appropriate.
3.3.1.5 Comply to developing procedures, policies and/or measures for the items shown in **Figure 2.** It is recommended to review and follow instructions detailed in ISSCR Guidelines for Stem Cell Research and Clinical Translation, NIH Guidelines for Human Stem Cell Research, and European Union Current Good Tissue Practice (CGTP).

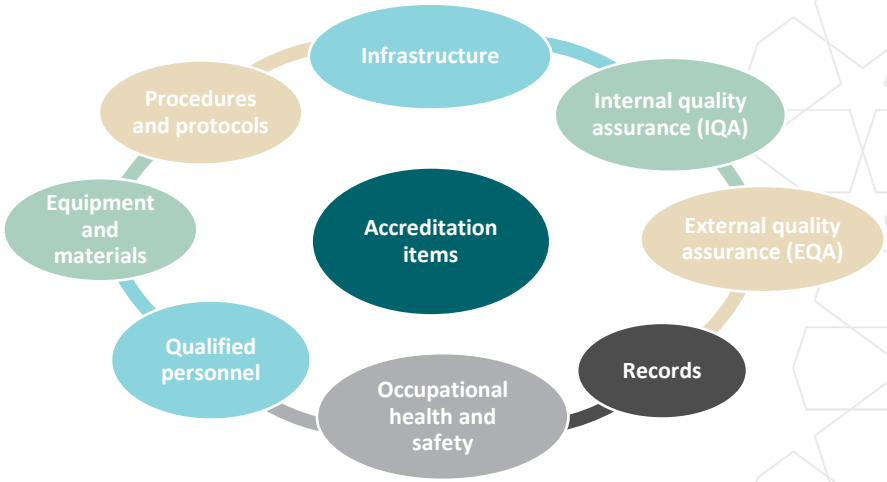

Figure 2. Required items to be covered for laboratory accreditation.

3.3.1.6 Comply to developing a Quality Management System that includes a quality manual and measures for internal and external quality assurance. (Refer to DOH Standard for Laboratory Accreditation for Genomic-Related Services and Products).
3.3.1.7 Provide evidence that the processes and technologies for the production, manipulation, and recovery of stem cells are internationally accepted and approved.
3.3.1.8 Guarantee and ensure the confidentiality of human donors to protect their rights and dignity.
3.3.1.9 Develop Standard Operating Procedures (SOPs) for every process performed during the handling of the stem cells, from the obtention of the biological specimen to intermediate products and to the final product. These documents must be as detailed as possible.
3.3.1.10 Stem cells, cells, and derived products must be properly labelled during all the manufacturing process.

3.3.2 Infection control program

The laboratory must implement strict quality control and infection control methods when processing stem cells and derivatives, for this the laboratory must:

3.3.2.1 Ensure efficient work with sterile equipment, suitable sample flow, and aseptic techniques.
3.3.2.2 Monitor compliance with rules and regulations of Good Laboratory Practice (GLP) and Good Tissue Practice (GTP).
3.3.2.3 Maintain adequate records of equipment and devices used for infection control and biovigilance. This equipment must be calibrated and monitored in accordance to DOH Standard for Clinical Laboratories.
3.3.2.4 Encourage and guarantee the mandatory use of biosafety cabinets, caps, masks, and sterile gloves.
3.3.2.5 Require hand cleaning between treatments and infection-free patients.
3.3.2.6 Periodically test personnel and donor samples for infectious diseases.

3.3.2.7 Ensure that patients must be free of any systemic infection, dental infection or periodontal disease.
3.3.2.8 Ensure that all biological samples are tested for the presence of infectious contaminants.

3.3.3 Infrastructure

To ensure a proper laboratory infrastructure, the laboratory must:

3.3.3.1 Ensure the facility is designed and constructed to meet international safety and biosafety standards for laboratories working with stem cells and to comply with DOH Clinical Laboratory Standards.
3.3.3.2 Have adequate lighting.
3.3.3.3 Have adequate ventilation in working environments.
3.3.3.4 Have adequate drainage and access to sinks and toilets.
3.3.3.5 Have adequate layout of the equipment facility.
3.3.3.6 Have adequate electrical safety.
3.3.3.7 Have adequate temperature.
3.3.3.8 Monitor and have measures for access control to the different areas, based on the established need.

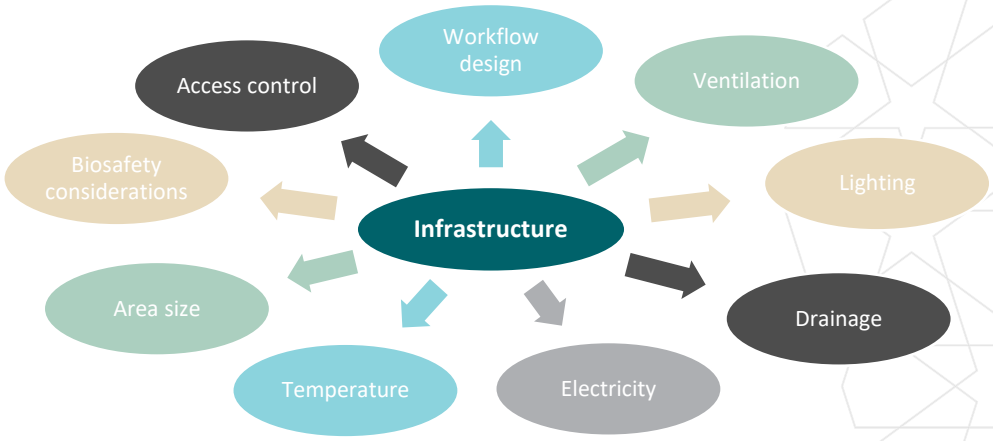

Figure 3. Considerations for a good infrastructure within a facility.

3.3.4 Environmental requirements

Environmental controls are required to guarantee equipment functioning and to prevent the contamination of stem cells, cells, tissues, and products during laboratory procedures. At the same time, these are necessary to prevent accidental exposures to biohazards and transmissible disease agents. Therefore, the laboratory must:

3.3.4.1 Monitor temperature and humidity controls daily.
3.3.4.2 Install ventilation systems and air filtration (e.g.: High Efficiency Particulate Air filtration)
3.3.4.3 Have an effective cleaning and disinfection program to ensure the integrity of the work environment.
3.3.4.4 Establish a plan for the safe disposal of biological and chemical waste.
3.3.4.4.1 Plan for waste disposal.
3.3.4.4.2 Plan for hazardous waste disposal.

3.3.5 Equipment

The following requirements for maintenance and calibration of laboratory equipment must be fulfilled:

3.3.5.1 Equipment used in the manufacture of stem cell- and cell-based products must be suitable for its intended function.
3.3.5.2 Localization of the equipment must comply with the environmental and infrastructure conditions stated by the manufacturer.
3.3.5.3 Equipment used for storage of reagents, cell lines, and stem cell-, cell-, and tissue-based products (e.g.: liquid nitrogen tanks, ultra-freezers) must have back-up equipment.

3.3.5.4 Regular maintenance, cleaning and calibration of the equipment must be performed and monitored to ensure proper functioning and accuracy of measurements in the production. These procedures must be described in well-defined and approved SOPs.

3.3.5.5 Ensure that the new equipment is clean and in good working condition before using it for any experiment.

3.3.5.6 Monitor equipment usage and promptly identify any equipment issues or malfunctions.

3.3.5.7 The use of the equipment and to detect and report any equipment problems or failures in a timely manner.

3.3.5.8 Maintenance of a well-organized record of equipment, programs, and materials used in testing, to ensure accuracy and quality. If a piece of equipment needs to be replaced, it must be done promptly, with the new equipment recorded in the appropriate registry.

3.3.6 **Reagents**

3.3.6.1 All reagents utilized for the manufacturing of stem cell-, cell-, and tissue-based products must be of clinical grade (pharmacopoeia grade).

3.3.6.2 If research grade materials are used, a quality control program must be included to test safety, purity, and potency of the materials.

3.3.6.3 Animal derived materials and reagents must be tested for adventitious agents.

3.3.7 **Personnel**

3.3.7.1 All laboratory personnel must be licensed by DOH and perform their activities in compliance with DOH Clinical Laboratory Standards, DOH Standard for Clinical Privileging of Healthcare Workforce and Clinical Services, DOH Healthcare Professionals Manual and Unified Healthcare Professionals Qualification Requirements (PQR).

3.3.7.2 To ensure the proper manipulation of stem cells, laboratory personnel must have a solid academic background in molecular and cellular biology, which could be supported by the completion of a relevant degree, specialization or approved course.

3.3.7.3 Laboratory personnel should have technical skills to manipulate stem cells and perform the necessary laboratory techniques for processing, such as cell culture, cryopreservation, purification and characterization of stem cells.

3.3.7.4 Personnel must be aware of and comply with regulations and standards governing the handling of stem cells for human use.

3.3.7.5 All personnel working with stem cells should be trained in the potential risks associated with stem cell handling, as well as in safety and risk prevention measures.

3.3.7.6 It is essential that personnel have a solid understanding of stem cell documentation, storage, and traceability to ensure patient safety and product quality.

3.3.7.7 Training and training procedures must be updated and evaluated regularly to ensure that all personnel maintain the necessary levels of competency.

3.3.7.8 Quality control and audits should be conducted to evaluate the effectiveness of training procedures and ensure that personnel can perform their duties safely and effectively.

3.3.7.9 Personnel should be trained in the safe use of equipment and appropriate personal protective equipment (PPE) should be provided.

3.3.8 **Biosafety**

3.3.8.1 A biosafety program must be established in accordance with national and international standards. (e.g.: NIH Biosafety in Microbiological and Biomedical Laboratories 6th edition, WHO Laboratory Biosafety Manual. 4th edition, WHO Biosafety Programme Management)

3.3.8.2 Biosafety measures should be implemented according to a risk assessment and laboratory procedures must attain to them during all the processes.

3.3.8.3 Infection control precautions must be established when handling human biological materials, stem cells and HCT/Ps.

3.3.8.4 It is mandatory that all personnel working in the stem cell laboratory are trained in the handling of biological materials and stem cells, as well as in the biosafety measures of the laboratory. All training must be documented.

3.3.8.5 It is mandatory to have established protocols for cleaning, disinfection, and waste disposal of biological materials.

3.3.8.6 It is mandatory to have separate and properly equipped work areas for the handling of biological materials and stem cells and to ensure that materials are handled in these areas exclusively to minimize the risk of cross-contamination.

3.3.8.7 All materials must be considered as potentially infectious during their manipulation.

3.3.8.8 A plan for managing, reporting, and monitoring incidental exposures to infectious diseases must be implemented.

3.3.9 **Storage**

3.3.9.1 The laboratory must develop and have standard operating procedures (SOPs) for the storage and release of human cell lines.

3.3.9.2 Reagents and stem cell-, cell-, and tissue-based products must be stored in the appropriate conditions (temperature, humidity, sterility) in GSP certified facilities/ rooms.

3.3.9.3 Measures to prevent mix-ups, contamination, and cross-contamination must be considered. (e.g.: labelling and characterization)

3.3.9.4 Temperature must be monitored and controlled.

3.3.9.5 Expiration date must be assigned to the stem cell-, cell-, or tissue-based product depending on:

- 3.3.9.5.1 Product type.
- 3.3.9.5.2 Processes performed.
- 3.3.9.5.3 Method of preservation.
- 3.3.9.5.4 Storage conditions.
- 3.3.9.5.5 Packaging.

3.3.10 **Receipt**

For all incoming stem cell-, cell-, and tissue-related material, the facility must:

3.3.10.1 Implement standard operating procedures (SOPs) for the reception of the material, including a quality control system.

3.3.10.2 Establish criteria to determine if the stem cell-, cell-, or tissue-based product can be accepted, rejected, or put in quarantine.

3.3.10.3 Evaluate the entering material for the presence of microorganisms and infectious diseases.

3.3.10.4 Perform and inspection for damage and contamination.

3.3.10.5 Comply with the informed consent requirements.

3.3.10.6 Ensure donor protection and privacy, in which a unique code is assigned to the biological material and all identifiable information is securely stored.

3.3.11 **Distribution and shipment**

3.3.11.1 Implement standard operating procedures (SOPs) for distribution and shipment of the products and materials.

3.3.11.2 The laboratory must determine criteria to prevent the transmission of communicable diseases prior to the distribution of the product.

3.3.11.3 The availability of products for distribution must be verified and documented, including information of the date of availability and verification results.

3.3.11.4 Products that are quarantined, contaminated, recovered from an ineligible donor, or do not satisfy pre-established requirements to prevent the transmission of infectious diseases must not be made available for distribution, unless approved by DOH with additional requirements.

3.3.11.5 The shipping containers and packaging must be designed and constructed to protect stem cell-, cell-, and tissue-based products from contamination and loss of cellular viability.

3.3.11.6 The laboratory must define appropriate shipping conditions that must be maintained during transit for each type of product based on a stability protocol.

3.3.12 **Genetic engineering**

3.3.12.1 Procedures related to genetics and stem cell handling must be performed by qualified personnel with expertise in molecular biology, bioengineering, genomics, and related subjects.

3.3.12.2 The laboratory must ensure that the processes have been performed under the quality control measures for the techniques described in the DOH Standard of Biotechnology and Bioinformatics in Medical Genomics.

3.3.13 **Release**

3.3.13.1 Measures to ensure that stem cell-, cell-, and tissue-based products are safe for human use must be adequately addressed, including procedures and specifications for the items described in **Table 3**.

3.3.13.2 The specifications must be determined depending on the characteristics of the product and its intended use. It is recommended to review the potential risks associated to the products in DOH Guidelines for Research and Clinical Translation in Stem Cells.

3.3.13.3 All products must comply with the specifications of identity, purity, safety, potency and traceability prior to its release.

Table 3. Release criteria for stem cell-, cell-, and tissue-based products destined for human use.

Release criteria	Description and examples
Identity: Product markers	Tests and assays that can corroborate the identity of the labelled product and distinguish it from others that are also processed in the same laboratory, during all phases of manufacture and handling. These must be performed periodically with validated assays, include acceptable limits, and monitor the desired function performance of the product. For example: - Identity markers from genotypic and/or phenotypic tests. - Cell surface antigens - Biochemical markers - Functional potency assays. - Morphology
Identity: Cellular components	Cellular components must be identified in relation to phenotypic and/or genotypic profile depending on the cell population and origin. For example: - Cell phenotyping markers: gene expression, antigen presentation, biochemical activity, among others. - Adherent cells: morphological analysis. - Allogeneic cells: histocompatibility tests, genetic tests. - Culture characteristics: phenotypic markers and stability.
Identity: Non-cellular components	Characterization and identity of all non-cellular components presents in the final product must be performed. For example: - Tests to characterize an active substance added in the process (if applicable). - Characterization and description of the composition and structure of supportive elements of the cellular components
Purity: integrity and contamination	Tests to corroborate that undesired materials in the final product do not exceed previously defined acceptable limits. For example: - Pyrogenicity assays due to endotoxins. - Quantification/Identification of residual proteins, peptides, reagents (e.g.: cytokines, growth factor, serum, among others). - Measurements of contaminating cell debris, different cell lineages or stages. - Tests for adventitious agents (PCR)
Purity: Viability	The viability of the cells must be quantitated and a lower limit for acceptability established. For example: - Ratio of viable/non-viable cells - Flow cytometry with DNA staining.
Potency	Tests to corroborate the biological activity of the product must be performed, based on its attributes and intended clinical application. For example: - Validated potency assays. - Surrogate markers. - Gene expression profiles. - Cell cloning. - PCR. - Immune mechanisms with multi-antigens formulations.
Tumorigenicity	Testing of chromosomal integrity and tumorigenicity of the product is mandatory due to the potential risks inherent of stem cells.

	- Karyotyping - Flow cytometry.
Traceability: Labelling and Packaging	The final product must be appropriately labelled and packaged, which must contain: - Product name. - Date of manufacture. - Cell concentration or number of cells. - Storage conditions. - Expiry date. - Non-personal patient identifiers. - Intended use. - Potential hazards associated.
Traceability: Shipping and Transport	Shipping and transport conditions must be clearly defined and monitored to maintain its integrity, sterility and potency. - Temperature - Packaging - Procedures for thawing in case of frozen delivery.

3.4 Prohibited procedures with stem cell-based therapies and products.

In the current state of scientific knowledge and understanding, application of the following areas is prohibited:

3.4.1 Clinical trials involving xenogeneic cells.

3.4.2 Clinical research on Xenogeneic-Human hybrids.

3.4.3 Use of genome modified human embryos, germ-line stem cells or gametes for developmental propagation.

3.4.4 Research involving implantation of human embryos (generated by any means) after *in vitro* manipulation, at any stage of development, into uterus in humans.

3.4.5 Modifying the nuclear genome of human embryos for the purpose of reproduction is premature and should not be permitted.

3.4.6 Use of mitochondrial (MRT) when other treatment options have not been applied and when no long-term follow up is possible.

4.Key stakeholder Roles and Responsibilities

4.1 DOH-licensed healthcare researchers, professionals, providers and 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. Insurers, TPAs and Medical Billing Offices.

4.2 Comply with the regulations established in this standard for health services, medical centers and research centers that develop activities related to this document.

4.3 DOH Guidelines for Research and Clinical Translation in Stem Cells should be considered as a basis in Abu Dhabi.

5.Monitoring and Evaluation

5.1 DOH monitors compliance with the normative established in this standard through audits that prepare supervision lists and reports evaluating the results and the impact of this standard on accreditation of laboratories for genomic-related services and devices.

5.1.1 DOH Audit will ensure compliance to this document after preparing a checklist generated based on this standard

5.2 This standard must be updated according to the changes made in the DOH documents cited in this standard and under prior authorization of the DOH.

6.Enforcement and Sanctions

6.1 Healthcare providers and medical laboratories must comply with the terms and requirements of this Standard.
6.2 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.

7. Relevant Reference Documents

No.	Reference Date	Reference Name	Relation Explanation / Coding / Publication Links

The guideline owner must clearly identify all documents and references related to the standard to ensure their compatibility with the standard and to facilitate the implementation process. Examples of relevant documentation and references include (but are not limited to):

- Other policies / standard / Scope of practice etc.
- Laws and regulations.
- International agreements or memoranda of understanding.
- Identification of legal articles related to the policy.
- Ministerial decisions or circulars.
- Titles of standard, scope of practices, methodologies, and manuals of operational work procedures.
- Any other documents (please specify).

The standard owner must ensure that the relevant stakeholders are consulted on these documents during the consultation process.

1	2020	DOH Standard on Human Subject Research.	https://www.doh.gov.ae/en/resources/standards
2	2020	DOH Guidelines for Conducting Clinical Trials with investigational products and medical devices.	https://www.doh.gov.ae/en/resources/guidelines
3	2021	Guidelines for Stem Cell Research and Clinical Translation	International Society for Stem Cell Research (ISSCR). (2021). https://static1.squarespace.com/static/611faaa8fee682525ee16489/t/62ed69b184e2ed258e6eb7e4/1659726257773/isscr-guidelines-for-stem-cell-research-and-clinical-translation-2021.pdf
5	2020	DOH Standard on Patient Healthcare Data Privacy	https://www.doh.gov.ae/en/resources/standards
6	2017	Indian Council of Medical Research. *National Guidelines for Stem Cell Research.* 2017.	http://www.icmr.nic.in/guidelines/Guidelines_for_stem_cell_research_2017.pdf
7	2018	ISO 20387:2018 Biotechnology — Biobanking — General requirements for biobanking	https://www.iso.org/obp/ui/#iso:std:iso:20387:ed-1:v1:en
8	2011	Current Good Tissue Practice (CGTP) and Additional Requirements for Manufacturers of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps)	https://www.fda.gov/regulatory-information/search-fda-guidance-documents/current-good-tissue-practice-cgtp-and-additional-requirements-manufacturers-human-cells-tissues-and

9	1991	WHO good manufacturing practices for biological products. Annex 3 of WHO Technical Report Series, No. 822	https://cdn.who.int/media/docs/default-source/medicines/norms-and-standards/guidelines/production/who-good-manufacturing-practices-for-biological-products.pdf
10	2017	COMPLIANCE PROGRAM GUIDANCE MANUAL Imported Human Cells, Tissues, and Cellular and Tissue-based Products (HCT/Ps)	https://www.fda.gov/media/73960/download
11	2017	Laboratory General Checklist CAP Accreditation Program	https://medicalcourier.com/wp-content/uploads/CAP-Lab-Master-Checklist-2017.pdf
12	2022	ISO 15189:2022 Medical laboratories – Requirements for quality and competence	https://www.iso.org/standard/76677.html
13	2018	Guidelines for Human Stem Cell Research Pursuant to Health and Safety Code 125118	https://www.cdph.ca.gov/Programs/CFH/DMCAH/HSCR/CDPH%20Document%20Library/HSCR-StemCellResearchGuidelines.pdf
14	2022	Approved Cellular and Gene Therapy Products	https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/approved-cellular-and-gene-therapy-products
15	2022	HCT/PS: Human cells, tissues, and cellular and tissue-based products	https://www.aabb.org/regulatory-and-advocacy/regulatory-affairs/regulatory-for-cellular-therapies/hctps
16	2020	Human medicines: regulatory information	https://www.ema.europa.eu/en/human-medicines-regulatory-information
17	2020	Five Decades Later, Are Mesenchymal Stem Cells Still Relevant?	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7058632/