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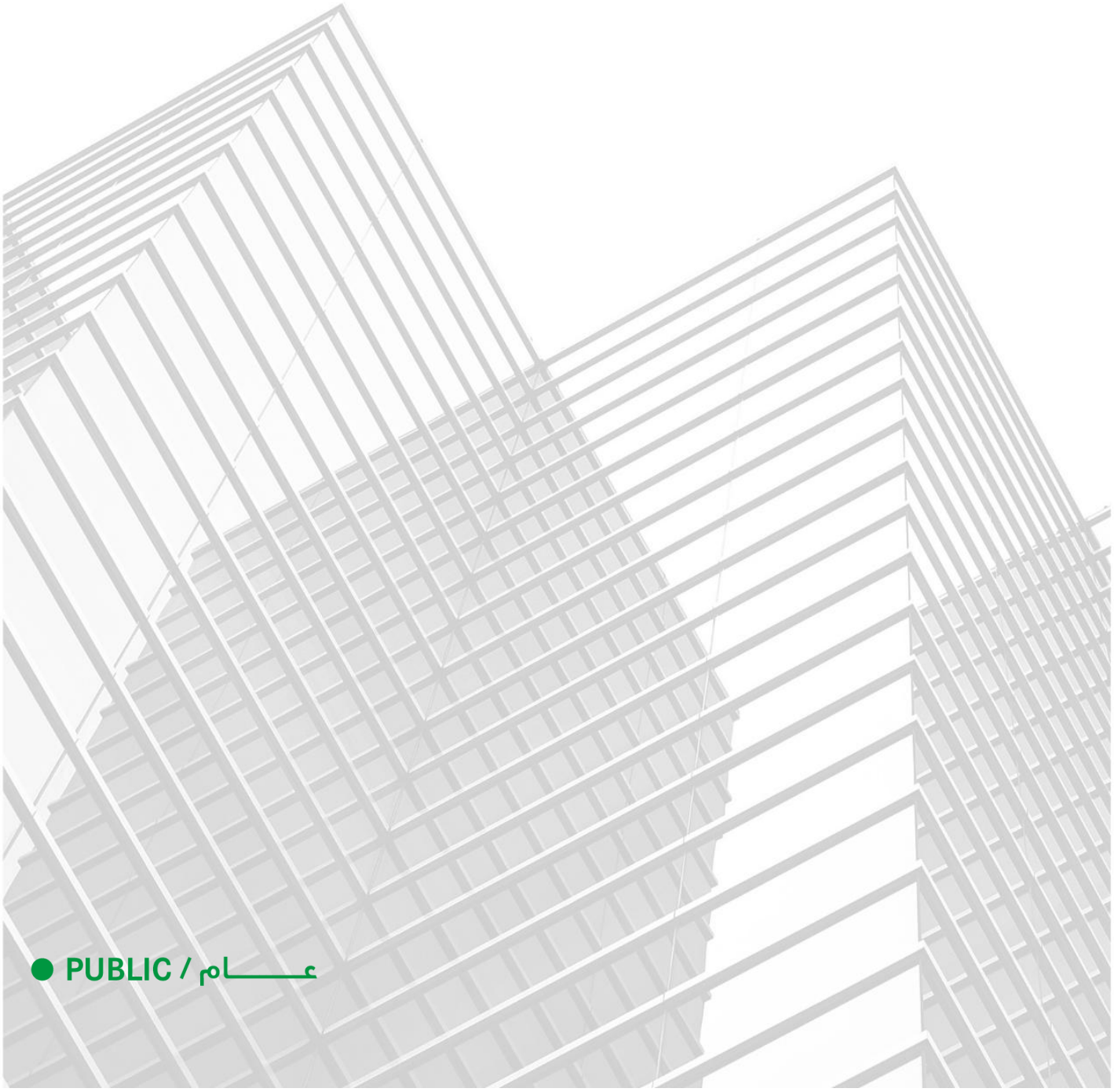
DEPARTMENT OF HEALTH

Standard for Therapies in Human Cell-Based, Tissue-Based, and Regenerative Medicine



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1. Standard Scope

The wide range of interventions intended for their regenerative properties is expanding rapidly in scope and application, increasingly blurring traditional regulatory boundaries and implying further challenges that need to be effectively regulated.

Many of these products, therapies, and devices are introduced with strong scientific rationale and high potential, others with less substantiated evidence are increasingly promoted for a wide spectrum of conditions. These range from autism and other neurodevelopmental disorders to regenerative medicine, metabolic health, and longevity. Their appeal is often heightened in areas where conventional or fully approved treatments remain limited or fail to deliver the outcomes patients are seeking.

Regenerative medicine, as defined by the U.S. Food and Drug Administration (FDA), encompasses approaches aimed at restoring, replacing, or regenerating cells, tissues, or organs to treat or mitigate disease. The FDA primarily regulates advanced therapies under this category, including minimally manipulated human cell- and tissue-based products, cellular therapies, engineered tissues, and gene therapies. However, many other products—both within and outside these categories—may claim to have a "regenerative effect," whether directly or indirectly. To ensure better governance and patient protection, this standard includes such products within its scope. Specifically, it covers blood components, minimally manipulated human cell and tissue products, subcellular structures, and compounds such as vitamins, peptides, and nucleotides that are known to stimulate natural repair processes.

The standard also applies to combination products that utilize these therapies or products to enhance the body's own healing mechanisms. At the same time, this standard excluded the Engineered Tissues, more than minimally manipulated cell therapies and gene therapies as each of these categories will have its own standard to be issued by DoH.

It is important to recognize that the rapid development and commercialization of regenerative medicine interventions raise unique scientific, ethical, and safety considerations. Regulatory agencies including DoH face increasing pressure to keep pace with innovations while ensuring that products on the market are both safe and effective. As a result, this standard was developed for the following purposes:

- To provide a regulatory tool to ensure rigorous oversight with ongoing vigilance to safeguard patient welfare and public trust in these emerging therapies.
- Ensuring adaptive frameworks, in a risk-based approach, to pave the way in the Emirate of Abu Dhabi to impactful innovation and research in the emerging modalities addressing unmet needs. This standard provides clear risk-based decision matrix per category of the therapies / medical products according to the international regulatory status, scientific rationale and level of evidence and according to the stage of development.
- Define clear boundaries for enforcement, what is strictly prohibited and what needs further approval from DoH to be allowed. It also defines violations and enforcement covering code of practice, communication with patients, promotion and advertising.

This standard covers the most emerging products that fall within its defined scope stratified by their regulatory class, following international guidelines on medical product classification rules. Class-based stratification is intended to cover most of the emerging products / therapies currently being promoted or in use for emerging medical uses such as longevity, well-being, and employing regenerative effects in new disease treatments. At the same time, the class-wise approach makes it flexible to cover with other future products expected to emerge internationally or developed locally in Abu Dhabi Emirate. Table 1 Provides the in-scope and out of scope in relation to this standard.

Table 1: In Scope and Out of Scope Therapies/ Medical Products			
Part	**Within Scope**	**Out of scope**	**Remarks**
Part One: Blood Components	Platelets Rich Plasma (PRP) Platelets Rich Fibrin (PRF) Conditioned Serum	Plasma, Albumin, platelets, coagulation factors and other Blood Products from donated source (not Autologous)	Autologous, minimally manipulated blood components intended for regenerative purposes are in scope. Donor-derived and industrially processed blood products are regulated under transfusion and biologics standards / and under Federal Pharmacy Law (No 38/ yr 2024) for Commercially available Bolod derivative Products
Part Two: Cell- Based & Tissue Based Products	A- Minimally manipulated for Homologous Use 1. **Adult or somatic stem cells include:** b.1 Hematopoietic progenitor /stem cells (HSCs). b.2 Mesenchymal stromal / stem cells (MSCs); 2**. Tissue-specific progenitor cells** with a more restricted differentiation capacity responsible for normal tissue renewal and turnover, such as neurons, intestine, skin, lung and muscle). 3. Structural Tissues: a. Adipose Tissue b. Others like cornea, bones, … **B-** Minimally Manipulated for Non-Homologous Use	A- Embryonic stem cells (hESCs) derived from blastocysts. *Xenogeneic (animal-derived) cells and tissues* i-More than Minimally Manipulated 1. induced pluripotent stem cells (iPSCs), and/or their intermediate stages, which are reprogrammed differentiated cells expected to re-acquire both the stemness and differentiation capacity of self-renewing embryonic stem cells. (considered more than minimally manipulated out of scope) 2. Cellular Advanced Therapies a. Immune effector cells b. Engineered Tissues *ii- Xenogeneic (animal-derived)* **3. Engineered Tissues**	Autologous and allogenic human cell-based / tissue-based products are under the scope of this standard as far as they are minimally manipulated whether intended for regenerative or for other uses. Perinatal sources are in-scope only when minimally manipulated. Stromal Vascular Fraction cells from Adipose Tissue are out of scope of this standard as considered more than minimally manipulated. The process of isolating SVF, whether through enzymatic (using collagenase) or mechanical methods, destroys the original structural integrity of the adipose (fat) tissue. The isolation process yields a "broth" of heterogeneous cells whose original related characteristics and function in the body have been significantly altered or are not fully understood for their new therapeutic uses.
		Gene Therapies 1. Gene-editing Technologies **2.** Nucleic acid–based therapies	

Table 1: In Scope and Out of Scope Therapies/ Medical Products			
Part	**Within Scope**	**Out of scope**	**Remarks**
Part Three: Sub-cellular structures	A. Exosomes (within scope): 1. Human-Derived Exosomes: a. Naïve b. Engineered 2. Animal -Derived Exosomes 3. Plant- Derived Exosomes Plant-Derived Exosomes (aka "Exosome-like nanoparticles")	Topical Plant derived exosomes for cosmetic claims Products don't contain mitochondria and claim Mitochondria boosting effect.	Note: Exosomes are classified according to their intended use, their route of administration and mechanism of action. They could be classified as cosmetic, medical device, biological and up to Gene therapies (Ex: Exosomes carrying recombinant mRNA encoding for the cystic fibrosis transmembrane conductance regulator protein and microRNA-17.) Exosomes products need to be classified to rule out if they are falling within the scope of this standard otherwise specifying the right standard to follow.
	Artificially engineered nanovesicles (beyond exosomes): Liposomes (artificial, lab-made vesicles composed of synthetic phospholipids and cholesterol, designed to mimic cell membranes).	Protein-based nanoparticles (Out of scope) Non-Biologic Nanomedicines" or "Nano-based medical products Ligand Therapies (nanoparticles carrying a cytotoxic drug with targeting ligands). **Polymeric micelles (out of scope):** Made of amphiphilic block copolymers (synthetic polymers). Used to solubilize hydrophobic drugs (e.g., paclitaxel micelles). Other Biologic Nano medicines / Nano based medical Products	
Part four: Compounds	Multivitamin and Trace Elements Drips / IV infusion / parenteral	Multivitamin and Trace Elements in Oral / Topical Dosage Form	
	Synthetic Peptides	Biologically derived peptides from living cells	
	Nucleotides	Nucleotides: Oral / Topical Dosage Form Biologically derived Nucleotides	

2. Definitions & Abbreviations

Definitions

No.	Term	Definition
2.1	Autologous Use	Cells / tissues/ organs/ blood/ blood component is taken from the patient and then transferred back into the same patient
2.2	Adipose tissue	Connective tissue composed of clusters of cells (adipocytes) surrounded by a reticular fiber network and interspersed small blood vessels, divided into lobes and lobules by connective tissue septa.
2.3	Advertising	Advertising includes promotional content, like websites, social media, TV/radio ads: It is information, other than labeling, that is intended to supplement, explain, or be textually related to the product including the statements of company representatives.
2.4	Advertisement	Advertisement includes: any statement, pictorial representation or design that is intended, whether directly or indirectly, to encourage /convince/ create demand on the use or supply of the subject of the advertisement, including the statements, pictorial representation or design on any material or content provided to public or patients. The intention referred to above is not only what the health facility or its in charge person responsible for the material intends, but also what the reasonable consumer views as being intended by the material. If the reasonable consumer considers that the material promotes the use or supply of subject of the advertisement, then the material is considered an advertisement. This definition applies to all forms of media, including traditional media (such as television, radio, print media and posters/displays) electronic media (such as websites, emails, blogs, discussion forums and social media). Additionally, material presented to the public through other means (e.g. workshops and education sessions) may meet the definition of advertising, depending on the content of the material.
2.5	Acceptable limits	Set of criteria (numerical limits, ranges, or other criteria for tests) to which a drug substance or drug product shall conform with to be considered acceptable for its intended use.
2.6	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.
2.7	Adult Mesenchymal stromal Cells	These cells are considered autologous and multipotent cells. Sources of Mesenchymal Stromal cells are found all over the body with the bone marrow producing a continual flow of “Mesenchymal stromal cells”. Fat has an abundant source of mesenchymal cells, and hematopoietic cells. Adult stem cells come from bone, cartilage, muscle, nerve tissue, blood vessels, connective tissue, and fat.
2.8	Allogeneic	Stem cells or tissue derived from different individuals other than the patient/subject himself/herself, that will be used for medical or research purposes, such as tissue repair or cell-based therapies.
2.9	Basic Function & same basic function or functions	The basic function of Human Cell / Tissue / blood components is what it does from a biological/ physiological point of view or can do when in its native state. “Basic” it means the function or functions that are commonly attributed to the human cell / human tissue / blood component as it exists in the donor.

		The "same basic function or functions" of Human cell / human tissue / blood component are considered to be those basic functions the human cell/ human tissue/blood component performs in the body of the donor, which, when transplanted, implanted, infused, or transferred, the human cell/ human tissue/blood component would be expected to perform one or more of these basic functions in the recipient. Basic functions of a structural tissue would generally be to perform a structural function for example, to physically support or serve as a barrier or conduit, or connect, cover, or cushion. Basic functions of a cellular or nonstructural tissue would generally be a metabolic or biochemical function, such as, hematopoietic, immune, and endocrine functions.
2.10	Cosmetic Claim	For the purposes of this standard, a Cosmetic claim is defined as any statement—whether explicitly presented on product or technology labels, within advertising materials, or implicitly communicated by treatment clinics—regarding the capacity of a medical product, therapy, technology, device, or procedure to improve the condition of the skin, hair, nails, eyes, or genitalia. Such claims include, but are not limited to, assertions related to hydration, enhanced appearance, or sustained aesthetic benefits. Claims for aesthetic improvements / enhancement resulting from higher-risk routes of administration, such as injectables, microneedling, invasive procedures, or laser treatments, are classified as medical rather than cosmetic claims.
2.11	Cellular/nonstructural tissue	Cells / Tissues that serve metabolic or other biochemical roles in the body such as hematopoietic, immune, and endocrine functions, are generally considered cells/nonstructural tissues.
2.12	Cell malfunction	Cells may not function properly, may fail to integrate, or may even cause abnormal growth or tumor-like behavior.
2.13	Compound	For the purposes of this standard, the term compound is used in the broad scientific sense as defined by International Union of Pure and Applied Chemistry (IUPAC) — a distinct chemical or biochemical entity with a defined structure — and corresponds to what regulatory agencies such as the US Food and Drug Administration (FDA) and European Medicines Agency EMA often call an 'active substance' or 'active pharmaceutical ingredient (API).' For the purpose of this standard, compounds will only include amino acids, peptides, nucleotides.
2.14	Compounding	The process of combining, mixing, or altering ingredients to create a medication tailored to the needs of a patient (38). Compounding is practiced under direct supervision of a UAE licensed pharmacist, in a UAE licensed compounding pharmacy. The traditional compounding process begins with a prescription created by the prescriber responding to a patient's need. The prescriber customarily chooses the active ingredient(s), dosage form, dose, dosing intervals, and route of administration when writing the prescription. The prescriber may also choose inactive ingredients, especially in cases where a patient has a documented allergy to an inactive ingredient. Compounded medications may offer therapeutic alternatives for patients with unique medical needs that cannot be met by authorized medicinal products in UAE.
2.15	Common Technical Dossier (CTD)	The agreement to assemble all the Quality, Safety and Efficacy information in a common format (called CTD - Common Technical Document) to standardize the information provided by the marketing authorization

		applicants to ensure comprehensive regulatory review processes and enable the implementation of good review practices. CTD is organized into five modules: Module 1 – Administrative information, ongoing safety monitoring and risk management plan for the drug product (Pharmacovigilance-PV) and prescribing information; Module 2 – Overviews and summaries of Modules 3–5; Module 3 – Quality (Chemistry, Manufacturing and Control (CMC)); Module 4: Non-clinical reports (pharmacology/toxicology animal and preclinical studies); Module 5: Clinical study reports.
2.16	Compassionate use	Treatment option that allows the use of an unauthorized 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 authorized therapies and who cannot enter clinical trials.
2.17	Critical process parameter (CPP)	Manufacturing process parameters that can influence CQAs. The CPPs that may affect potency-related CQAs must be identified and must be monitored or controlled. These CPPs need to be within appropriate pre-determined limits.
2.18	Critical Quality Attributes (CQAs)	CQAs in drug development are the physical, chemical, biological, or microbiological properties of a drug product that must be controlled within defined limits to ensure the product's safety, efficacy, and overall quality. These attributes are identified early in the development process and serve as the foundation for a Quality by Design (QbD) approach.
2.19	Dietary supplement	A medical product taken by mouth or applied topically that contains vitamins, minerals, amino acids, peptides, enzymes, botanicals, or other substances intended to supplement the diet and offered only for health claims.
2.20	Exosomes	Extracellular vehicles (EVs): tiny lipid-bound particles secreted by cells that contain proteins, RNA, DNA fragments, and lipids.
2.21	Full Life Cycles of Human Stem Cell Based and Human Tissue based Therapies	Consist of the three primary functions within a cellular therapy program: the Collection Facility, Processing Facility and Clinical Program.
2.22	FACT standards	Standards Issued by Foundation for the Accreditation of Cellular Therapies: These Standards incorporate sound principles of quality medical and laboratory practice in cellular therapy. However, no standards can guarantee the successful outcome of such therapies. FACT-JACIE Standards are minimal guidelines that may be exceeded as deemed appropriate by the personnel responsible in individual facilities. Directors and Medical Directors assume responsibility for adopting FACT-JACIE Standards as appropriate to the program, and for setting more rigorous internal requirements where appropriate. Attempts have been made to conform these Standards to existing United States federal regulations and the requirements of the European Union Directives; however, compliance with these Standards does not guarantee compliance with all applicable regulations.
2.23	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.
2.24	Good Manufacturing Practice (GMP)	System that guarantees controlled manufacturing of products in accordance with quality standards.

2.25	Good Tissue Practice (GTP)	Set of quality standards and guidelines that govern the collection, processing, storage, and distribution of human tissues for medical use. Current (GTP) - referred to it as cGTP- ensures that tissues are safe, effective, and traceable, and that they meet regulatory requirements.
2.26	GXP	GxP is a general abbreviation for the "good practice" quality guidelines and regulations. The "x" stands for the various fields, including pharmaceutical, Bio Research, Manufacturing, Laboratory, Clinical, Documentation etc.
2.27	Genetically modified chimeric antigen receptor cells (CAR cells)	An immunotherapy that uses a patient's own lymphocytes which are genetically engineered to recognize and kill cancer cells. This includes both NK-CAR and CAR-T cells.
2.28	HLA typing	is the laboratory process of identifying the genetic variations of the human leukocyte antigen (HLA) system that regulates immune recognition. In stem cell-based / tissue-based therapies transplantation, HLA typing is the essential test to determine whether a donor's stem cells are compatible with a recipient's immune system. • Genes typed: At minimum, HLA-A, -B, -C (class I) and HLA-DRB1, and HLA-DQ (class II) (10/10) Many centers also include HLA-DP for high-resolution matching. • Goal: Reduce the risks of graft rejection and GVHD by selecting donors whose HLA alleles are as close as possible to the recipient's. • Resolution levels: o *Low/intermediate resolution* (broad antigen group). o *High resolution* (allele-level sequencing, current standard in HSCT). • Techniques: PCR with sequence-specific primers/probes, next-generation sequencing (NGS), or Sanger sequencing.
2.29	Hematopoietic Cell Transplantation (HCT)	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).
2.30	Hematopoietic stem/progenitor cells (HPCs)	Sources of hematopoietic stem/progenitor cells (HPCs) include cord blood, peripheral blood, and bone marrow
2.31	Human cellular and tissue-based products	Articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient.
2.32	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.
2.33	Homologous use	The repair, reconstruction, replacement, or supplementation of cells or tissues with a human cell based / Tissue based therapy that performs the same basic function or functions. Could be either autologous or allogeneic. There are other conditions for homologous use see full section under (15.2)
2.34	Health Claim	Describes a relationship between a food substance (a food, food component, or dietary supplement ingredient), and reduced risk of a disease or health-related condition. A health claim can be approved only after a review and evaluation of scientific evidence, either from existing literature or robust clinical studies submitted by the medical product developer, manufacturer, or marketer.

2.35	Labeling	Includes the Human Cell Based / Tissue based Therapy label and any written, printed, or graphic materials that supplement, explain, or are textually related to the product, and which are disseminated by or on behalf of its manufacturer.
2.36	Longevity Claim	For the purposes of this standard, a longevity claim is defined as any statement—whether explicitly stated on product or technology labels, included within advertising materials, or implicitly conveyed by treatment clinics—regarding the ability of a medical product, therapy, technology, device, procedure, personalized treatment strategies or personalized treatments to prevent or delay chronic conditions such as heart disease, cancer, and Alzheimer's disease, or to achieve an extension of health span through targeting aging process or enhancing functional capacity to enhance overall quality of life during those extended years.
2.37	Manipulation (cell / Tissue manipulation)	Cell/ Tissue manipulation is defined as the process covering range of interventions using various tools and technologies carried out on the cell / either for the purpose of isolation, selection or for altering / controlling the cellular / tissue behaviors and properties.
2.38	*Matching donor for stem cells*	Is a person whose HLA profile (please refer to definition of HLA typing 2.28) closely corresponds to that of the recipient, ensuring the recipient's immune system will accept the transplanted stem cells / tissue and minimize the risk of graft rejection or graft-versus-host disease (GVHD). • Ideal donors: Siblings have a 25% chance of being a full HLA match. If no family match is found, registries are searched for unrelated, compatible donors. • Other compatibility checks: ABO blood type and infectious disease screening are considered, but HLA matching is the cornerstone for hematopoietic stem cell donation suitability.
2.39	Matching Donor in Tissue Transplantation	Conventional tissues (skin, cornea, bone, cartilage, heart valves): • HLA matching plays a smaller role compared to HCT. • For corneal transplantation, for example, HLA typing has limited predictive value; immune privilege of the cornea makes matching less critical. • For skin allografts, HLA mismatch can cause rejection if the graft is permanent, but temporary grafts (e.g., burn dressings) may be used regardless of match. • For bone, cartilage, tendons, heart valves, the tissue is often decellularized or processed to reduce immunogenicity, so matching is less strict. • Main requirement: ABO blood group compatibility and infectious disease screening.
2.40	Matching Donor in Engineered Tissues	Engineered or regenerative tissues (e.g., bioengineered skin, trachea, cartilage, vascular grafts): • If created from the patient's own cells (autologous): No need for HLA typing or donor matching (no rejection). • If created from allogeneic donor cells (another person's cells): Immunologic matching may matter, but engineered tissues are often decellularized or combined with biocompatible scaffolds to minimize immune response.

		• Emerging Techniques: o Universal donor cells (gene-edited to lack major HLA molecules). o Immune evasive scaffolds that may prevent recognition. o Induced pluripotent stem cell (iPSC) banks where partial HLA matching is attempted.
2.41	Minimal Manipulation:	Processing does not change the cell's fundamental biological characteristics and original function. Examples include isolation, washing, centrifugation, and trimming, but generally excludes culturing.
2.42	Medical Claim / indication	For the purposes of this standard, a medical claim refers to any assertion, whether explicitly stated on the product / therapy label / advertisement or implicitly conveyed by the treating clinic, concerning the ability of a medical product, therapy, technology, device or procedure to treat, prevent, or cure a disease or support longevity. It also encompasses statements promising substantial improvement in the condition or function of an organ (such as skin, liver, or brain). This definition further extends to aesthetic or rejuvenation claims presented as producing immediate visible results, including those associated with injectable products.
2.43	Non-homologous use	Intended therapeutic use of cells / tissues outside their native physiological context, such as the transplantation of hematopoietic cells or mesenchymal stromal cells into the heart or brain
2.44	Off-label use	Use of approved pharmaceutical drugs for an unapproved indication or in an unapproved age group, dosage, or route of administration.
2.45	Parenteral (Invasive)	Administration by injection, infusion, or implantation by passing the Gastrointestinal system and 1st pass effect.
2.46	Perinatal source of cells and tissues	Refers to the collection of the placenta and extraembryonic structures, such as the umbilical cord and amniotic fluid/membrane, which are usually discarded after birth, to obtain various cell types (including stem cells) for therapeutic and regenerative medicine applications.
2.47	Pluripotent stem cells	Highly potent type of stem cell with the ability to self-renew and differentiate into all cell types of the adult body (excluding extra-embryonic tissues like the placenta). They are fundamental to early embryonic development, existing in the blastocyst stage as embryonic stem cells (ESCs), but can also be generated from adult cells through reprogramming.
2.48	Processing of Human Cell Based / Tissue	Any activity performed on a Human Cell / tissues other than recovery, donor screening, donor testing, storage, labeling, packaging, or distribution, such as testing for microorganisms, preparation, sterilization, steps to inactivate or remove adventitious agents, preservation for storage, and removal from storage. Processing also includes cutting, grinding, shaping, culturing, enzymatic digestion, and decellularization.
2.49	Product characterization and identifying CQAs.	Assessing a broad range of product attributes to understand the properties of the product / therapy more completely. Starting from the earliest stages of product development, product characterization studies is recommended to better understand the product's MOA and to help identify product attributes that may be potency-related CQAs. Characterization data is important when assessing manufacturing changes. Assays used in characterization studies do not necessarily need to be qualified, but they must be scientifically sound and fit for their intended

		purpose, be sufficiently precise to detect meaningful differences in product attributes and provide results that are reliable.
2.50	Promotion	Promotion / Marketing directed to healthcare professionals either directly or using channels strictly targeting only healthcare professionals and not exposed to public (ex: medical Journals and medical conferences).
2.51	Potency Testing for cell based medical products	According to the ICH guideline 6QB, potency is the quantitative measure of biological activity based on the attribute of the product, which is linked to the relevant biological properties. The assay demonstrating biological activity shall be based on the intended biological effect which ideally be related to the clinical response. Two types of potency assays: 1) in vitro assays using cell systems and 2) in vivo assays using animal models.[56]
2.52	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.
2.53	Repair, reconstruction, replacement, or supplementation of a recipient's cells or tissues	Repair generally means the physical or mechanical restoration of tissues, including by covering or protecting. Reconstruction generally means surgical reassembling or re-forming. Supplementation generally means to add to, or complete. Repair, reconstruction, replacement, and supplementation are not mutually exclusive functions, and a human cell- based / tissue-based therapy could perform more than one of these functions for a given intended use.
2.54	Structural tissue	Tissues that physically support or serve as a barrier or conduit, or connect, cover, or cushion are generally considered structural tissues.
2.55	Somatic Cell	Any cell type of an organism other than reproductive cells.
2.56	Stem Cell	Undifferentiated and unspecialized cell 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.
2.57	Immune Effector Cells (IECs)	Defined by FACT as cells, in vitro modified or not, that have differentiated into a form capable of modulating or effecting a specific immune response. This includes T cells, tumor infiltrating lymphocytes (TILs), natural killer cells, dendritic cells, and mesenchymal stromal cells. Final products include, but are not limited to, genetically modified chimeric antigen receptor T cells (CAR-T cells), CAR-NK cells, genetically modified cord blood, gene-edited products, and dendritic cell vaccines. Hematopoietic progenitor cells that differentiate into immune effector cells are also within the scope
2.58	Tissue chimerism	A situation where the transplanted cells behave differently from the host tissue, resulting in a "mixed" or mosaic tissue (cells with different genetic/epigenetic programming coexisting).
2.59	Tissue-specific progenitor cells	Partially differentiated cells found within specific tissues or organs that have a limited capacity for self-renewal and are generally restricted to differentiating into the mature, specialized cells of that particular lineage. Their primary function is to maintain tissue homeostasis and repair damage

		in response to injury (e.g., satellite cells in muscle regenerating muscle fibers, neural progenitor cells form neurons and glia).
2.60	Tissue Factor	A protein that plays a critical role in blood clotting, TF (also known as thromboplastin, coagulation factor III, F3 or (CD142) is a transmembrane glycoprotein receptor for coagulation factors VIIa and X with a molecular weight of 47 kDa is located on the different cells. TF can initiate blood coagulation upon binding to FVIIa. Tissue Factor/CD142 Antibody recognizes endogenous levels of total Tissue Factor/CD142 protein.
2.61	Topical Route of Administration	Administration to a particular spot on the outer surface of the body.
2.62	Unmet medical need (UMN)	a commonly used term to describe therapeutic areas that require additional attention, where current therapeutic offerings are not yet available in Abu Dhabi and internationally or not satisfactory either for being comparatively less effective, pose higher risk or much more expensive for similar results.
2.63	USP Chapter 797	a set of minimum standards from the US Pharmacopeia (USP) for sterile compounding of pharmaceutical products to ensure patient safety and product quality. It addresses potential risks like microbial contamination, incorrect ingredient strength, and the use of substandard ingredients in compounded sterile preparations (CSPs). The chapter sets guidelines for environmental control, proper procedures, and personnel competency in healthcare settings preparing CSPs for humans and animals.
2.64	USP <71> Sterility Tests	a chapter in the US Pharmacopeia that details the official methods for testing if pharmaceutical products and medical devices labeled as "sterile" are, in fact, free of microbial contamination. It ensures product safety by verifying the absence of viable microorganisms like bacteria, yeasts, and molds, using specific procedures like membrane filtration or direct inoculation with media that support aerobic and anaerobic growth.
2.65	USP <788> for subvisible particulate matter in injectable drugs	a standard from the US Pharmacopeia that sets the required testing procedures for subvisible particulate matter in injectable drugs to ensure patient safety. It outlines two methods for detecting these particles—light obscuration and microscopic assay—and specifies the limits for the number of particles allowed in both large-volume and small-volume parenteral products.
2.66	USP <85> (LAL/BET)	The limulus amebocyte lysate Test, under the USP <85> Bacterial Endotoxins Test (BET) chapter, provides the basis for detecting such contaminants in these products. The article provides a comprehensive insight into the LAL test, its importance and how this test ensures that products are safe for human use
2.67	Validation	a mandatory requirement by regulatory bodies for new drug submissions, diagnostic approvals, and environmental monitoring protocol. Process validation: a quality assurance method that involves collecting and evaluating data to prove that a manufacturing / manipulation process consistently produces the intended outcome (whether intermediate product or final product) that meets predetermined specifications and quality attributes. It is a systematic approach that involves three key stages: process design, process qualification, and continued process verification. The goal is to ensure product quality, safety, and compliance with regulations like Good Practices (GxP). Lab test validation: a critical process in quality assurance that confirms a laboratory test performs as intended, ensuring accuracy, reliability, and regulatory compliance. This involves assessing a test's analytical

		performance characteristics (such as accuracy, precision, and specificity) against predefined criteria, and documenting all steps and results to provide confidence in the data produced.
2.68	Wharton's jelly	a gelatinous connective tissue found in the umbilical cord that protects blood vessels from compression and torsion. It is rich in mesenchymal stem cells (MSCs), which are of significant interest in regenerative medicine due to their immunosuppressive, proliferative, and differentiating properties. The jelly also contains extracellular matrix components such as collagen, hyaluronic acid, and chondroitin sulfate

Abbreviations

No.	Abbreviation	Term
2.69	ADHRTC	Abu Dhabi Health Research and Technology Committee (or its equivalent)
2.70	AI	Artificial intelligence
2.71	ATMPs	Advanced Therapy Medicinal Products
2.72	CQAs	Critical Quality Attributes
2.73	CPP	Critical process parameter
2.74	COO	Country of Origin
2.75	CTD	Common Technical Dossier
2.76	cGTP	Current Good Tissue Practice
2.77	DoH	Department of Health Abu Dhabi
2.78	EMA	European Medicines Agency
2.79	FACT	Foundation for the Accreditation Of Cell Therapies
2.80	FDA	Food and Drug Administration
2.81	GCP	Good Clinical Practices
2.82	GMP	Good Manufacturing Practices
2.83	HLS	Health Life Science
2.84	HSCs	Hematopoietic progenitor /stem cells
2.85	HSCT	Hematopoietic Stem cell Transplantation
2.86	MSCs	Mesenchymal stromal cells
2.87	IRB(s)	Institutional Review Board(s)
2.88	Pharmaco-Vigilance	PV
2.89	QMS	Quality Management System
2.90	R&D	Research and Development
2.91	RWE	Real-World Evidence
2.92	UMN	Unmet Medical Need
2.93	WHO	World Health Organization

3. Standard Requirements and Specifications

Part 1: Blood Components (Platelets Rish Plasma (PRP), Platelet-rich fibrin (PRF) & Conditioned serum)

3.1 Introduction and Definitions (Blood Components (Platelets Rish Plasma (PRP), Platelet-rich fibrin (PRF) & Conditioned serum):

3.1.1 For the purposes of this document, blood component therapies intended for regenerative applications include Platelet-Rich Plasma (PRP), Platelet-Rich Fibrin (PRF), and conditioned serum.

3.1.2 Blood component therapies are derived from human blood and undergo concentration processes to increase levels of growth factors and anti-inflammatory cytokines[1]).

3.1.3 These products are normally used in an "autologous" manner, which means the blood is first collected from a patient, processed in the laboratory / clinic and then the resultant layer is returned to the same patient.

3.1.4 Commercially supplied kits and equipment designed for the processing of collected human blood under aseptic conditions must be pre-approved by reference regulatory authority as medical devices for preparing blood component therapies.

3.1.5 The main difference is that PRP (Platelet-Rich Plasma) contains a high concentration of platelets for a rapid, immediate release of growth factors, while PRF (Platelet-Rich Fibrin) creates a fibrin matrix that releases growth factors gradually over a longer period. Conditioned serum is a separate substance from a blood collection that, after clotting, has no platelets but is rich in cytokines secreted by white blood cells.

Table 2: The Difference Between Blood Component Therapies for Regenerative Use

Feature	Platelet-Rich Plasma (PRP)	Platelet-Rich Fibrin (PRF)	Conditioned Serum (ACS)
Preparation	Processed with an anticoagulant at higher centrifugation speeds to separate platelets from other blood components.	Prepared without anticoagulants at a lower centrifugation speed. This allows a natural fibrin scaffold to form.	Prepared by incubating blood with special glass beads to stimulate the production of anti-inflammatory proteins.
Composition	Concentrated platelets and growth factors suspended in plasma.	Concentrated platelets, growth factors, white blood cells, and a natural fibrin matrix.	High concentration of anti-inflammatory proteins, especially interleukin-1 receptor antagonist (IL-1Ra), but without platelets.
Healing Mechanism	Releases a high concentration of growth factors very quickly, triggering an immediate and rapid healing response.	The natural fibrin matrix acts as a scaffold, releasing growth factors and other beneficial cells slowly over an extended period.	Blocks inflammatory cytokines (proteins) that cause pain and tissue damage, targeting inflammation at its root.
Use Case	Often used for faster results in cosmetic / aesthetic procedures like microneedling and treating early-stage hair thinning.	Favored for deep skin rejuvenation, under-eye hollows, and for therapies that require longer-term tissue regeneration.	Used primarily for musculoskeletal conditions like osteoarthritis and spinal pathologies to reduce inflammation and pain.
Duration of effect	Shorter duration of effects due to the quick release of growth factors.	Longer-lasting effects due to gradual, sustained release of healing factors from the fibrin matrix.	Can provide longer-lasting pain relief by addressing the underlying inflammation.

3.2 Preparation of Blood Component Therapies for Regenerative Use

3.2.1 Preparation of Platelets Rich Plasma (PRP)

3.2.1.1 PRP is prepared from 10-60 ml blood collected into a syringe containing an additive (anticoagulant) to prevent the blood from clotting. Either acid citrate dextrose or sodium citrate solution to prevent coagulation and premature secretion of the alpha granules[2].

3.2.1.2 In order to isolate the liquid, cell-free plasma, the blood tube is generally centrifuged to separate the red blood cells (RBC; erythrocytes), with the platelets and white blood cells (WBC) remaining in the upper layers of the plasma.

3.2.1.3 The next steps to collect the PRP layer vary between individual protocols but are intended to discard the plasma layer not containing platelets (PPP; platelet-poor plasma) and leave the PRP layer.

3.2.1.4 Activated PRP: Some studies induced growth factor secretion and degradation of alpha granules by adding calcium gluconate, calcium chloride, or thrombin before administration There is no consensus as to whether platelets must be activated exogenously or use host thrombin as endogenous activator in order to maximize the therapeutic effect[2].

3.2.1.5 The platelet alpha granules secrete growth factors within 10 minutes after clotting or activation, so PRP shall be used within 10 minutes of activation for maximum benefits.

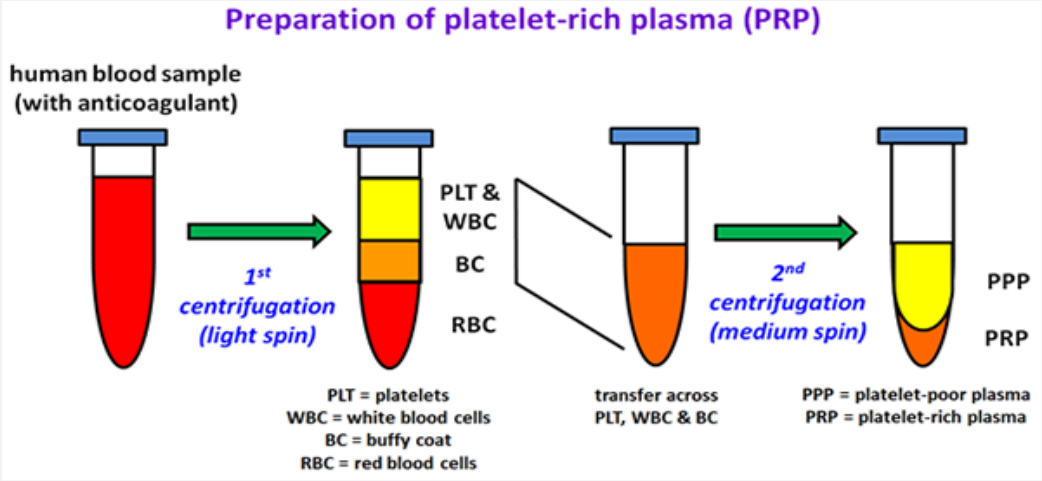


Figure 1: Illustrating the preparation of platelet-rich plasma (PRP) in four steps, with four test tubes shown side by side [1].

3.2.2 Preparation of Platelet-rich fibrin (PRF)

3.2.2.1 PRF is a second-generation PRP where platelets and WBC form a fibrin matrix (scaffold) that claims to localize growth factors and increase their concentration.

3.2.2.2 Like PRP, PRF is prepared from a blood collection, but no anticoagulant is added, and the blood is swiftly centrifuged after collection (≤ 2 minutes) to isolate the fibrin matrix.

3.2.2.3 After centrifugation, the upper layer contains PPP, the PRF matrix is in the middle layer, with RBC at the bottom.

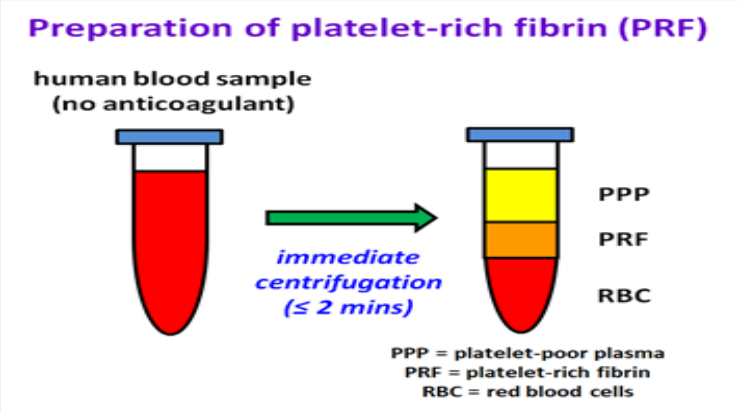


Figure 2: Preparation of Platelets Rich Fibrin (PRF)[1]

3.2.3 Preparation of Conditioned Serum[1]

3.2.3.1 Like PRP and PRF, conditioned serum is prepared from a blood collection, but the blood is allowed to naturally clot (no anticoagulant).

3.2.3.2 In order to isolate the liquid serum, the blood tube is centrifuged to separate the blood clot. The serum fraction does not contain platelets.

3.2.3.3 In contrast to PRP and PRF, which uses centrifugation to separate the blood components, the blood tube is then incubated for a period of time in the laboratory to allow for full activation of WBC and the secretion of cytokines into what is known as conditioned serum.

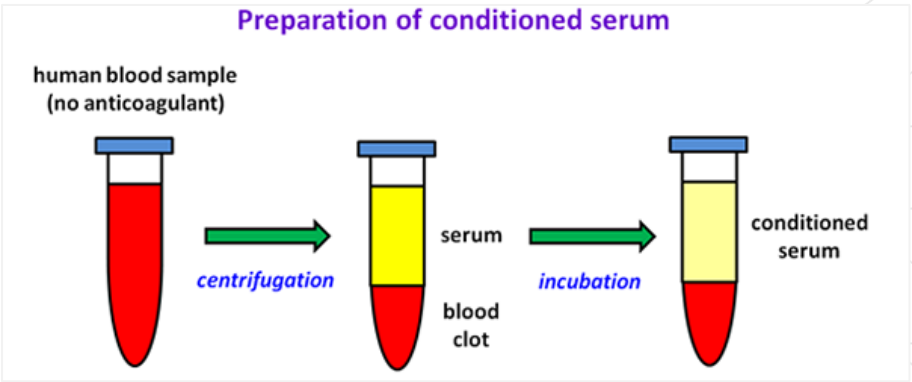


Figure 3: Preparation of Conditioned Serum.[1]

3.3 Platelets Rich Plasma PRP – Classification

3.3.1 Platelet-rich plasma, also known as platelet-rich growth factors or platelet concentrate, is a concentrate of platelet-rich plasma protein derived from whole blood, centrifuged to remove red blood cells.

3.3.2 Other components of PRP: In addition to the main component that contains high concentrations of platelets, there are also other components, such as, the presence or absence of leucocytes and platelet-activating agents, which are used to define different types of PRP.

3.3.3 Classification of Platelet Rich Plasma: More than one standardization method is proposed, the most important ones are mentioned below:

3.3.3.1 DEPA proposed by Magalon et al, based on four components: dose of injected platelets (baseline concentration of platelets at 200×109/L), efficiency of the process (platelet recovery rate %), purity of PRP (relative composition in platelets %) and activation process, (61) as shown in Table 3. From this classification, an "AAA" DEPA score is referred to a high-concentration platelet injection (>5 billion) with minimal red blood cell contamination and well prepared with a proper method resulting in minor loss of platelets from whole blood. The last category in the DEPA classification is reporting the presence or absence of any exogenous activator, such as thrombin or calcium chloride.

Table 3: DEPA Score is Categorized in Order from A to D[3]

Dose of Injected Platelets (Billions)	**Efficiency of the Process (Platelet Recovery Rate %)**	**Purity of the PRP (Relative Composition in Platelets %)**
A >5 very high dose	A >90 high	A >90 very pure PRP
B 3–5 high dose	B 70–90 medium	B 70–90 pure PRP
C 1–3 medium dose	C 30–70 low	C 30–70 heterogeneous PRP
D <1 low dose	D <30 poor	D <30 whole blood PRP
***Abbreviations**: DEPA; dose of injected platelets, efficiency of production, purity of the PRP, activation of the platelet-rich plasma.		

3.3.3.2 PLRA (Platelets, Leukocyte, Red Blood Cells Activation) by Mautner et al.[4]: a more accurate classification in terms of platelet concentration, presence/absence of leukocytes and red blood cells (RBC), and the presence of activators.

3.3.3.3 MARSPILL (Method, Activation, Red Blood Cells, Spin, Platelets, Image guidance, Leukocytes, Light activation) By Lana et al. 5 a more accurate classification emphasized the role of mononuclear cells, such as monocytes and lymphocytes, which belong to the PBMCs (peripheral blood mononuclear cells) group. These cells stimulate the regeneration of the tissues by cytokine release.

3.3.3.4 It is important to note that there are several different kits available on the market, enabling the preparation of PRP solution with different platelets concentrations and additional ingredient content; accordingly, the classification system need to be consistent to standardize the blood component therapy across the administration.

3.4 PRP Mechanism of Action

3.4.1 Currently, many studies have demonstrated that platelets not only affect hemostatic system, but also affect inflammatory system, angiogenesis, stem cell induction, and cell proliferation through the release of many different growth factors and cytokines[6,7,8,.]

3.4.2 The idea behind using PRP is that the plasma-platelet mixture is rich in the growth factors and cytokines released from their alpha granules[2,6,9] which, in theory, could provide a biological boost to the body's own healing processes, as they are known to promote soft tissue healing, stimulate cell growth, division, and differentiation, reduce inflammation, fight infection, and provide immunity against pathogens. Thus, it is argued, PRP may also be effective in speeding tissue regeneration and treating inflammation.

Table 4: Overview of active ingredients of PRP[2,9]

Growth factors	Origins	Physiological effects
Platelet-derived endothelial growth factor (PDGF),	Neuronal cells, astrocytes, oligodendrocytes, and vascular cells	Induces stem cell differentiation, participates in neuroprotection, and promotes cell proliferation and migration
Transforming growth factor β (TGF-β),	B cells, T cells, dendritic cells, macrophages[10]	Promoting cell proliferation and differentiation, participating in tissue repair and fibrosis, and inhibiting the activation of immune cells
vascular endothelial growth factor (VEGF)	Production by endothelial cells, smooth muscle cells, platelets, neutrophils and macrophages	In charge of angiogenesis and vascular repair, indirectly promoting tissue repair and neuroprotection
insulin-like growth factor-1 (IGF-1)	Hepatic stellate cells, osteoblasts, fibroblasts, macrophages	Promotes growth, cell differentiation and cell proliferation
fibroblast growth factor-2 (FGF-2) & bFGF	Endothelial cells, bone cells	Induction of neovascularization and neurotrophy
epidermal growth factor (EGF)	Endothelial cells, vascular smooth muscle cells, neutrophils, macrophages	Promoting wound healing and anti-inflammatory

3.4.3 Additional factors in PRP[2]

3.4.3.1 Glial cell line–derived neurotrophic factor (GDNF),

3.4.3.2 In addition, PRP can induce the proliferation of dermal papilla (DP) cells by activating extracellular signal-related kinase (ERK), fibroblast growth factor 7 (FGF-7), beta-catenin, and Akt signaling (an anti-apoptotic signaling molecule).

3.4.3.3 There is also an increase in expression of Bcl-2 protein (an anti-apoptotic protein) in vitro human dermal papilla cells cultured with PRP.

3.4.4 Factors impacting effectiveness of stimulating tissue regeneration:

3.4.4.1 The concentration of platelets present in plasma is the main factor impacting the effectiveness of PRP therapy. Several studies have shown that

concentration two to six times higher than normal platelet count is required for optimal outcomes[2].

3.4.4.2 The variety of growth factors and cytokines found in the PRP that can accelerate wound healing and tissue restoration[2].

3.4.4.3 PRP preparation Kits: There are several types of commercial PRP kits that simplify PRP preparation. However, these Kits vary in the type of collection tubes, power used, the number of cycles and the duration of centrifugation and the activation method applied. Accordingly, the resulting PRP differs in platelet concentrations, the presence of leukocytes and platelet activator leading to the diversity of growth factors concentration.[2].

3.4.5 The abovementioned clauses explain the challenge behind standardizing the treatments of PRP and the variability in the clinical benefits of PRP reported in the literature.

3.5 Contraindications to PRP and Other Blood Component Therapies

3.5.1 Although autologous PRP and other blood component therapies covered by this standard are only allowed to be prepared using authorized kits and instrumentation (authorized by the relevant authority as per medical device regulations) and under the right conditions that prevent contamination of the blood, is considered a safe treatment with minimal side effects, there are several contraindications that need to be considered before treatment.

3.5.2 Absolute contraindications to PRP and other blood component therapies include:

3.5.2.1 critical thrombocytopenia

3.5.2.2 Platelet dysfunction

3.5.2.3 Hemodynamic instability

3.5.2.4 Sepsis,

3.5.2.5 local infection (site PRP)

3.5.2.6 Hepatitis C, HIV/AIDS, Hepatitis B and HTLV-I/II

3.5.2.7 Blood Cancers

3.5.2.8 cardiovascular diseases requiring blood thinners

3.5.2.9 Anyone with cancer in the area being treated shall not receive it.

3.5.3 Relative contraindications to PRP and other blood component therapies include[2]

3.5.3.1 NSAIDs use in 48 hours,

3.5.3.2 Glucocorticoid injection at treatment site within one month

3.5.3.3 Systemic glucocorticoid within 2 weeks

3.5.3.4 Recent illness or fever

3.5.3.5 Cancer, especially bone or hematolymphoid

3.5.3.6 Anemia (hemoglobin less than 10 grams per deciliter)

3.5.3.7 Thrombocytopenia (platelets less than 150,000 per microliter)

Tobacco use

3.6 PRP Adverse Effects[8,11]

3.6.1 Infection is one of the most frequently reported issues after PRP injection. While localized infections and leg ulcers can occur, however, studies showed PRP injections do not significantly increase the risk of joint infection. discrepancies between these

findings may stem from bacterial contamination during PRP preparation, as well as differences in injection sites.

3.6.2 Visual disturbances have also been reported in some patients after PRP treatment. While rare, such disturbances can occur soon after the procedure or within a few days, with delayed onset possible for up to two weeks. This underscores the importance of extended postoperative monitoring.

3.6.3 As PRP relies on growth factors and platelets for its effects, individuals with coagulation disorders, such as those with coronary artery disease or cerebral infarction, may face an increased risk of vascular obstruction post treatment

3.6.4 Nicotine and alcohol addiction can elevate blood viscosity and cause platelet aggregation. Such patients must be assessed for heightened risk of adverse effects before undergoing PRP therapy.

3.6.5 Most common adverse effects, including temporary and tolerable pain during treatment, mild headache, minimal itching, transient erythema and edema on treated area. No major side effects such as scarring, infections, panniculitis, hematoma or allergic reaction have been documented following PRP treatment[2]

3.6.6 Healthcare professionals and Healthcare Facilities prescribing PRP and other Blood Component therapies, need to report Adverse Drug Reaction according to the outlined conditions and procedures set out by DoH for Pharmacovigilance.

3.7 Patient Assessment and Communication

3.7.1 PRP shall only be considered after a thorough evaluation and confirmation that the patient is in a safe state of health, which will help minimize the incidence of complications

3.7.2 Prior to treatment, healthcare providers shall evaluate the patient's health status, considering potential issues such as cardiovascular disease or infections that may impact on PRP efficacy.

3.7.3 Clear and comprehensive communication with patients regarding expected outcomes, potential risks, and the experimental nature of PRP is necessary to manage their expectations effectively.

3.7.4 Patient selection and a tailored treatment approach are vital in PRP therapy, necessitating a personalized plan to maximize therapeutic efficacy and patient satisfaction. The following need to be considered:

3.7.4.1 Age and overall health: the physiological responses and healing capacities of PRP vary significantly across age groups. Additionally, comorbidities or chronic diseases can impact PRP's effectiveness. Studies found that younger, healthier patients experienced shorter healing times with PRP for complex wounds.

3.7.4.2 The nature and severity of the condition: Most PRP used in clinical practice is derived from autologous blood components, and the preparation process for mild injuries can impose additional trauma and financial strain. For severe injuries, it remains unclear whether PRP retains its therapeutic effects due to changes in blood composition from loss or stress, and preparation may worsen the original condition. Research indicates that higher platelet concentrations lead to better outcomes in knee osteoarthritis treatment.

3.7.4.3 Before undergoing PRP, it is crucial to conduct a comprehensive assessment of the patient's risk factors. These factors include, but are not limited to, allergy history, bleeding tendencies, and other potential health issues.

3.8 Uses of PRP, Regulatory Approvals & Evidence

3.8.1 It is important to note that reference regulatory bodies such as the US-FDA, EMA and others have not approved PRP as a specific treatment for any condition. While many PRP preparation systems have FDA / CE clearance for specific uses, such as enhancing bone graft handling, this clearance is not the same as an FDA / EMA approval for the PRP treatment itself.

Table 5: PRP Applications (many applications require additional evidence to be considered effective PRP treatment options)

Application / Indication	Use / Rationale	Evidence Level / Strength	Key Caveats / Uncertainties
Osteoarthritis (especially knee OA)	Intra-articular injection to reduce pain, improve function, slow degeneration	Moderate evidence from RCTs & meta-analyses, but mixed results. [12]	Heterogeneity in PRP preparation, dosing, blinding. Some well-designed trials show little difference vs placebo (e.g. JAMA trial)[13]
Tendinopathies / Chronic tendon disorders (e.g. lateral epicondylitis, Achilles tendinopathy, patellar tendinopathy, rotator cuff tendinopathy)	Inject into or around the tendon to stimulate healing, reduce inflammation	Variable evidence: moderate in some (e.g. lateral epicondylitis)[14]; but some meta-analyses report no significant benefit over placebo in many tendinopathies [15]	Differences in patient selection (acute vs chronic), PRP formulation, control arms; high heterogeneity[15]
Muscle, ligament, soft tissue injuries / sports medicine	To speed healing of strains, tendon tears, ligament sprains	Mostly lower-level evidence (case series, small trials) and less robust RCT data. [16]	Difficult to isolate effect; placebo and natural healing confounders; standardization lacking
Hair loss / Alopecia (androgenetic alopecia, alopecia areata, etc.)	Inject or apply PRP to scalp to stimulate hair follicles, increase hair density	Some small RCTs and meta-analyses suggest benefit (hair density, thickness) over placebo or controls, but overall evidence is still emergent. [2]The PRP can increase the survival of hair follicle cells through anti-apoptotic effects and stimulate hair growth by extending the anagen phase of the hair cycle.	Many studies showed promising results for Hair Loss. Lack of large, long-term RCTs; variation in protocols (frequency, concentration); publication bias possible[2] The use for alopecia areata scarring alopecia don't have adequate scientific support yet.
Wound healing / Dermatology / Skin regeneration / Plastic surgery	Use in ulcers, burns, surgical wounds, skin rejuvenation, scar modulation	Mostly lower to moderate evidence from small studies, pilot trials, dermatologic case series.[9]	Variability in outcomes; control comparisons often lacking; more high-quality RCTs needed[2,9]

Oral & maxillofacial / Dental surgery	Use in extraction sockets, bone grafts, sinus lifts, periodontal defects to enhance bone & soft tissue healing	Some RCTs / meta-analyses with moderate evidence for improved soft tissue healing / early bone fill, though long-term benefit less certain [9,17]	Differences in surgical technique, adjunct biomaterials; high cost vs. benefit debate
Reproductive medicine / Fertility / Endometrium / Ovarian "rejuvenation"	Intrauterine PRP to improve endometrial thickness / receptivity; intraovarian injections to boost ovarian reserve	Emerging use, largely observational / pilot studies; very preliminary evidence[18,19] In recent meta-analysis[19] None of the included studies was RCT, so it carries a high risk of bias. Most of the studies did not report clinically significant outcomes such as clinical pregnancy and live birth rates. Even the studies that reported these outcomes failed to compare them either to before intervention nor to controls.	High risk of bias, small sample sizes, lack of controls, need for rigorous trials. The main limitations of the presented research so far are that different kits and methods were used to prepare the PRP solution and drawing of final conclusion is difficult and burdened with technical bias[18] There is marked heterogeneity among the included studies regarding the study design, baseline hormonal levels, timing of PRP injection, the time for the outcomes assessment and reporting of outcomes[19].
Adjunct to surgery / Tissue engineering	Use PRP in grafts, scaffolds, to enhance bone, cartilage, tendon repair in surgical settings	Preclinical and translational data are strong; clinical evidence variable	Standardization, dose, timing, delivery all need exploration; regulatory and reproducibility issues[55]
Ophthalmology[58] autologous serum and platelet-rich plasma eye drops		The level of evidence for PRP in ophthalmology varies by condition. While some conditions, such as macular holes and dry eye disease, show promising results, larger-scale studies are still needed to establish clear clinical guidelines	High risk of publication bias, limited number of studies.

3.8.2 In general, DoH allows PRP therapies for autologous use in Abu Dhabi under the supervision of specialized physicians provided the following conditions are met:

3.8.2.1 The healthcare facility must secure all necessary approvals for PRP therapy service licensing under the Healthcare Facility License. The license will specify permitted PRP uses based on the clinic's preparedness, as well as the physician's specialty and experience.

3.8.2.2 PRP must be administered strictly for autologous use, following a comprehensive patient assessment to identify and rule out any

contraindications. DoH prohibits the administration of non-autologous plasma or blood component therapies for regenerative or longevity claims (ex: young plasma or plasma obtained from the blood of youth aged healthy donors).

3.8.2.3 Patients must sign a comprehensive consent form containing all necessary details to ensure traceability to the patient, including diagnosis, intended purpose of use and the expected effects, side effects, contraindications.

3.8.2.4 The procedure must be performed by physicians who are DoH licensed in the specialty relevant to the intended use.

3.8.2.5 PRP is prepared from patient blood using instruments, Medical Devices, or systems that are certified by a recognized regulatory body such as the US FDA or hold CE certification, the certification / clearance shall specifically mention the intended use of PRP preparation for the patient (for example: Medical Device has clearance for preparing PRP for enhancing bone graft handling).

3.8.2.6 The PRP therapy must not be advertised for any application under any circumstances without obtaining appropriate approval from DoH and relevant authorities.

3.8.2.7 Clinics providing PRP to patients must adhere to Current Good Tissue Practices (CGTP) and Good Manufacturing Practice (GMP) standards.

3.8.2.8 The DoH prohibits PRP mixtures that include exogenous growth factors, hormones, or other drugs without proper medical product approval from reference authority and EDE.

3.9 Application Process for Allowing Provision of Therapies Utilizing PRP / PRF & Conditioned Serum in Abu Dhabi Healthcare Facilities

3.9.1 The following PRP indications are not required to undergo a detailed therapy application process for approval of the specific therapy, provided that all other requirements outlined in 'part one' and its subsections are met by the DoH licensed healthcare facilities offering these services:

3.9.1.1 The application of platelet / Serum therapy for cosmetic and aesthetic purposes, such as skin rejuvenation and hair growth stimulation (important note: alopecia areata & scarring alopecia are excluded and are required to be fully evaluated upon the application submission as explained in below sections).

3.9.1.2 The use for improving joints mobility ex: Osteoarthritis (ex. Knee and ankle OA), however this will need a proper HTA evaluation for reimbursement decisions.

3.9.1.3 If PRP, PRF, or conditioned serum products undergo more than minimal manipulation, they may be regulated as biological products rather than blood components. The examples provided below are not exhaustive.

3.9.2 If PRP, PRF, or conditioned serum products undergo more than minimal manipulation, they may be regulated as biological products rather than blood components. The examples provided below are not exhaustive.

3.9.2.1 If the PRP, PRF or conditioned serum product is prepared using any compounds that alter the plasma, serum, or other blood components (e.g.

coatings on a blood tube that activates a blood component), this would be considered more than minimal manipulation of the blood and subjected to higher regulation.

3.9.2.2 Similarly, if the PRP, PRF or conditioned serum product is cultured in the incubator with other cells, tissues, growth factors, or other ingredients prior to use, the products are unlikely to meet the definition of PRP, PRF or conditioned serum and could then be subjected to regulation as a biological.

3.9.3 The utilization of PRP, PRF or conditioned serum for medical treatments (including alopecia areata, scarring alopecia) beyond the above-mentioned indications (in 3.9.1) require direct and explicit authorization from DoH. The clinic must submit an application detailing the specific application of the PRP to DoH, including the following documentation:

3.9.3.1 Comprehensive details regarding the therapy, including its purpose, usage, and supporting scientific rationale.

3.9.3.2 A thorough literature review.

3.9.3.3 Provision of the usage protocol, eligibility criteria, and follow-up procedures.

3.9.3.4 Comprehensive risk analysis and risk management plan, endorsed by the Pharmacovigilance (PV) section of the DoH.

3.9.3.5 Description of the method of preparation, instruments and kits employed, along with their respective certifications.

3.9.3.6 Information on the source of expertise and any relevant partnerships, including credentials of know-how providers, where applicable.

3.9.3.7 Submission of curriculum vitae for physicians overseeing the treatment, detailing their qualifications specific to the therapy and its indication; these documents are required for endorsement by Healthcare Professional Licensing.

3.9.3.8 Explanation of the clinic's system for maintaining traceability and ensuring data integrity.

3.9.3.9 Successful completion of the DoH audit, specifically addressing the therapy application, is mandatory prior to DoH decision issuance.

3.9.4 The **Department of Health (DoH)** may grant one of the following types of approvals for the provision of PRP, PRF or conditioned Serum therapy (will be referred to as Blood Platelet / Serum Therapies) within the Emirate:

3.9.4.1 **Full Approval**

Full approval may be granted when the Blood Platelet / Serum Therapy has demonstrated acceptable levels of safety, efficacy, and quality in accordance with recognized international standards and DoH requirements. Clinics providing fully approved therapies must hold a valid DoH healthcare facility license and ensure that all associated healthcare professionals are appropriately licensed by DoH and competent to administer the therapy.

3.9.4.2 **Approval for Experimental or Investigational Blood Platelet / Serum Therapy**

Where the Blood Platelet / Serum Therapy is still under clinical evaluation or lacks sufficient regulatory credentials to support full authorization, the DoH may grant an approval for experimental or investigational use

3.9.4.2.1 The approval for Experimental / investigational for Blood Platelet / Serum Therapy would be subject to the following conditions:

3.9.4.2.1.1 The therapy and its clinical protocol shall obtain prior ethics approval from the DoH Concerned Committee.

3.9.4.2.1.2 The clinic providing therapy must be recognized by the DoH as a Clinical Research Center authorized to conduct human biomedical research.

3.9.4.2.1.3 The clinic shall ensure full compliance with the DoH Standards for Human Biomedical Research, Good Clinical Practice (GCP) principles, including requirements for informed consent, patient safety monitoring, data integrity, and adverse event reporting.

3.9.4.2.1.4 Patient follow-up and outcome monitoring must be conducted in accordance with the approved protocol and any additional conditions specified in the therapy approval.

3.9.4.2.2 Approval of experimental therapy may be issued under one of the following categories:

3.9.4.2.2.1 **Compassionate Use (outside clinical trial framework) (Appendix 1)** still needs ethics approval and to follow the relevant procedure and conditions set by DoH for compassionate use.

3.9.4.2.2.2 **Conditional Approval**

3.9.4.2.2.2.1 Permits the provision of the therapy for unmet medical need to eligible patients under a clinical research framework where preliminary evidence supports potential safety and benefit.

3.9.4.2.2.2.2 Clinics may be authorized to charge reasonable fees for the approved therapy, as defined by DoH.

3.9.4.2.2.2.3 Conditional approval shall be time-limited and renewable, subject to submission of interim data and evidence of satisfactory safety and performance outcomes.

3.9.4.2.2.2.4 Upon demonstrating adequate evidence of safety and efficacy, the clinic may apply for transition to Full Approval.

3.9.4.2.2.3 **Approval under the Clinical Trial Framework:** Applies when the therapy does not address an unmet medical need and requires additional evidence for full approval.

3.10 Blood Component Therapies Advertisement, Promotion and Responsible Practice

3.10.1 Patients should only decide to undergo PRP after fully comprehending the procedure, its benefits, potential risks, and alternative options. Patients lacking comprehensive understanding of PRP prior to treatment may lead to less cost-effective medical decisions. PRP requires to be approached cautiously, following adequate preclinical

studies and rationalization to prevent unnecessary physical and economic harm to patients.

3.10.2 Clinics and healthcare providers are mandated to refrain from marketing or advertising PRP under any circumstances.

3.10.3 It is essential for clinics, healthcare professionals and patients to recognize that PRP has not yet received approval from any recognized authority for its current uses. Although there is scientific rationale supporting its use in many indications, its efficacy has yet to be established in well-controlled clinical trials for the majority of applications. Many regulatory bodies, like US FDA Health Canada, EMA and others classify PRP treatments as experimental.

3.10.4 PRP exaggerated claims of its regenerative properties can create unrealistic patient expectations. Healthcare providers have an ethical obligation to manage these expectations by presenting accurate information about the variability of PRP's efficacy and the supporting evidence. This approach helps patients maintain realistic treatment and outcome expectations. Healthcare practitioners are required to use responsible, evidence-based statements that do not exploit patients' vulnerabilities or desperation. Research indicates that PRP varies significantly based on preparation methods and individual differences, with even batches from the same person showing considerable discrepancies in growth factor content and platelet concentration. Thus, the therapeutic effects of PRP must not be overstated to patients. Consent forms clarifying the treatment and its expected outcomes are required.

3.10.5 The evidence base for PRP is still developing, with no consensus on its efficacy for certain applications. Health care providers must stay updated on the latest research and effectively communicate this evolving evidence to patients, ensuring treatment decisions are informed by the most reliable information.

3.10.6 It is important to note that there are substantial variations in the preparation methods and level of processing used to manufacture these products, so the level of regulation applicable must be carefully considered.

3.10.7 The intended clinical use of the PRP, PRF or conditioned serum product must be justified based on proven evidence of safety and efficacy.

3.10.8 Where equipment such as commercially supplied kits are used in the preparation of a PRP, PRF or conditioned serum product, it may also be subject to regulation as a medical device.

Part 2: Human Cell Based & Human Tissue Based Therapies

3.11 Introduction to Human Cell Based & Human Tissue Based Therapies

3.11.1 Definition: Human Cell Based & Tissue Based Therapies articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient.

3.11.2 Donation of human cell / tissues for allogenic use is allowed as far as the donor is signing consent forms. Consent form should be approved by DoH for compliance with ethical standards.

3.11.3 Part 2 of this standard is a replacement of "DoH Standard for Stem Cell Therapies Products and Regenerative Medicine" and needs to be read in conjunction with the other relevant and applicable regulations issued by the DoH.

Regulation	Applicable to
Human Biomedical Research Guideline	Conditions and procedures to be followed in case the therapy was granted approval in Clinical trial framework or conditional approvals.
Policy on Biobanking	Applicable to collection, processing, and preservation of human stem cells and human tissues
Standard for Pan-Human Biobanks	Applicable to collection, processing, and preservation of human stem cells and human tissues
Standard on Biobanking for Stem Cells	For Processing and cryopreserving stem cells
Guidelines for HCT Indications and Timing of Referral for Adult and Pediatric	Applicable to the administration of Human Stem cell transplantation
Guidelines for Clinical & Translational Research in Stem Cells	This guideline provides recommendations for conducting safe, effective and sustainable stem cell research and its translation into clinical practice by maintaining compliance with policies and legal norms of Abu Dhabi and international ethical principles. It does not describe all the requirements and processes; it is recommended to review related policies and standards published. It also provides the conditions for off label use and compassionate use.
Precision Medicine Policy Clinical Use and Research, Data, Ethics and Public Engagement	Applicable to the patient care process within clinics offering any form of precision medicine.
Standard for Centers of Excellence in Hematopoietic Stem cell Transplantation (HSCT) Services for Adults and Pediatrics	For the facility licensing and applying for Center of Excellence
Standard for the production of Human Platelet Lysate (hPL) for the manufacture of cell-based and gene therapy medicinal products for human use	Not applicable: the hPL use for culturing stem cells will lead to more than minimally manipulated human cell based medicinal product.

3.11.4 Human Cell & Tissues used in Human Cell-Based & Tissue- Based Therapies according to function are divided into two types:

3.11.4.1 **Structural Tissues:** Structural tissues are tissues intended for implantation, transplantation, infusion, or transfer into a human recipient. Tissues that physically support or serve as a barrier or conduit, or connect, cover, or

cushion are generally considered structural tissues. Vascularized organs are out of scope. Examples of structural tissues include bone, skin, amniotic membrane and umbilical cord, blood vessel, adipose tissue, articular cartilage, non-articular cartilage, and tendon or ligament.

3.11.4.2 **Cells/nonstructural tissues**: Cells and tissues that serve metabolic or other biochemical roles in the body such as hematopoietic, immune, and endocrine functions, are generally considered cells/nonstructural tissues.

Examples: Reproductive cells or tissues (e.g., oocytes), hematopoietic stem/progenitor cells (e.g., source cord blood), lymph nodes and thymus, parathyroid glands, peripheral nerve and pancreatic tissue.

Note: Secreted body fluids (e.g., amniotic fluid) are generally not considered within the scope of cells/ nonstructural tissue. Cells from secreted body fluids are generally considered within the scope and the definition of cells or nonstructural tissues would apply.

3.11.4.2.1 **Cells (Stem cells)**

Stem Cells can be defined as undifferentiated and unspecialized cell 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. For this standard, stem cells include:

3.11.4.2.1.1 Embryonic stem cells (hESCs) derived from blastocysts;

3.11.4.2.1.2 Adult or somatic stem cells include:

3.11.4.2.1.2.1 Hematopoietic progenitor /stem cells (HSCs);

3.11.4.2.1.2.2 Mesenchymal stromal cells (MSCs);

3.11.4.2.1.3 Tissue-specific progenitor cells with a more restricted differentiation capacity responsible for normal tissue renewal and turnover, such as neurons, intestine, skin, lungs and muscle).

3.11.4.2.1.4 Induced pluripotent stem cells (iPSCs), and/or their intermediate stages, which are reprogrammed differentiated cells expected to re-acquire both the stemness and differentiation capacity of self-renewing embryonic stem cells.

3.11.4.2.2 **Characteristics of stem cell according to type:**

3.11.4.2.2.1 Human Embryonic stem cells (hESC)[20]: Use of this type of stem cell is out of scope of this regulation. For early-stage research researchers shall apply for DOH Ethics and Human Biomedical Research committee and approvals and institutional review boards (IRBs) approvals.

3.11.4.2.2.1.1 Derived from the inner cell mass of a blastocyst-stage embryo (very early developmental stage).

3.11.4.2.2.1.2 Can be maintained in vitro as established cell lines.

3.11.4.2.2.1.3 hESCs are pluripotent and have the capacity to differentiate to virtually every cell type found in the human body.

3.11.4.2.2.1.4 hESCs can be characterized by a distinct set of cell surface markers, as well as marker genes for pluripotency.

3.11.4.2.2.1.5 hESCs, when transplanted into a permissive host form teratomas, benign tumors consisting of various cell types derived from all three germ layers: endoderm, mesoderm and ectoderm.

3.11.4.2.2.1.5 Teratoma formation is a standard test in research to confirm that a cell line is truly pluripotent. However, it also implies a safety concern: if undifferentiated hESCs are transplanted into patients, they might form teratomas instead of integrating safely.

3.11.4.2.2.1.6 Clinical use of hESCs requires rigorous differentiation protocols and purification to avoid undifferentiated cells causing tumors.

3.11.4.2.2.1.7 hESCs can be differentiated in vitro using either external factors in the culture medium, or by genetic modification. However, in vitro differentiation often generates cell populations with varying degrees of heterogeneity.

3.11.4.2.2.1.8 The use of induced pluripotent stem cells (iPSCs) as an alternative to hESCs, is encouraged, since iPSCs provide pluripotent cells without the ethical concerns linked to embryo destruction, while still carrying similar risks of tumorigenicity if not properly controlled.

3.11.4.2.2.2 Adult or somatic stem cells : Use of this type of stem cell is out of scope of this regulation. For early-stage research researchers shall apply for DOH Ethics and Human Biomedical Research committee and approvals and institutional review boards (IRBs) approvals.

3.11.4.2.2.2.1 Hematopoietic stem cells (HSCs):

3.11.4.2.2.2.1.1 HSCs are a specific class of tissue-specific stem cells. They can give rise to differentiated cells of all hematopoietic lineages, myeloid and lymphoid, either in the haemopoietic bone marrow or in the thymus.

3.11.4.2.2.2.1.2 HSCs are derived from:

3.11.4.2.2.2.1.2.1 placental and cord blood at birth in concentrations like levels found in adult bone marrow.

3.11.4.2.2.2.1.2.2 In the adult body, HSCs are localized in the red bone marrow and found circulating at a lower frequency in the peripheral blood.

3.11.4.2.2.2.1.2.3 They may also be found at low frequency in other tissues (liver, spleen and muscle) but their origin and relevance for normal hematopoiesis remains to be fully determined.

3.11.4.2.2.2.1.3 HSCs are mobilized to the blood compartment after treatments with intensive chemotherapy (or sometimes radiation therapy) and/or growth factors.

3.11.4.2.2.2.1.3.1 Growth factors (like G-CSF / filgrastim, or GM-CSF) are given. These stimulate the bone marrow to produce more stem cells. They also loosen the “anchors” that keep HSCs in the marrow, allowing them to enter the blood.

3.11.4.2.2.2.1.3.2 Chemotherapy (intensive regimens) damages marrow cells temporarily. As the marrow recovers, HSCs are “pushed out” into the bloodstream as part of regeneration. Once mobilized, the HSCs can be collected by apheresis (a blood draw process that separates stem cells from circulating blood).

3.11.4.2.2.2.1.3.3 Also with Plerixafor that works by blocking the CXCR4 receptor, disrupting its interaction with SDF-1α, which mobilizes hematopoietic stem cells from the bone marrow into the bloodstream.

3.11.4.2.2.2.1.4 HCT is the most effective treatment for a broad spectrum of hematopoietic malignancies as well as non-malignant congenital and acquired disorders. Since there is often a disparity between the number of HSCs needed by the patient and those available from the donor, an effective in vitro amplification prior to HCT is required[21].

3.11.4.2.2.2.1.4.1 CD34+ is a protein marker found expressed on the surface of HSCs and less mature progenitor cells. CD34 is the most commonly used cell surface marker to identify human HSCs.

3.11.4.2.2.2.1.4.2 HSCs are characterized by a range of parameters, including an increased ability of HSC self-renewal and proliferation and maintaining their pluripotency.

3.11.4.2.2.2.2 Hematopoietic stem cells (HSCs):

3.11.4.2.2.2.2.1 MSCs are primarily derived from bone marrow stroma or adipose tissue. Additionally, MSCs have been isolated from numerous other tissues, such as retina, liver, gastric epithelium, tendons, synovial membrane, placenta, umbilical cord and blood and currently only clinically approved indication is for GVHD, and rest of the use is in clinical trials.

3.11.4.2.2.2.2.2 MSCs are defined by adherence to plastic, specific surface antigen expression and multipotent differentiation potential.

3.11.4.2.2.2.2.3 MSCs are lineage-committed cells as they can differentiate towards mesenchymal lineages, mainly adipogenic, osteogenic and chondrogenic cell lineages.

3.11.4.2.2.2.2.4 Under appropriate culture conditions in vitro differentiation of MSCs to tenocytes, skeletal myocytes, astrocytes and neurons has been described.

3.11.4.2.2.2.2.5 Mechanism of Action: The application of MSCs as a form of cell therapy is based on their ability to regulate the inflammatory response and participate in tissue repair and regeneration processes. In response to inflammatory stimuli, MSCs secrete a multitude of immunomodulatory factors, chemokines, and growth factors that regulate the tissue immune microenvironment and facilitate tissue regeneration.

3.11.4.2.2.2.2.6 Potential Uses if evidence under establishment conclude as satisfactory: Most trials focused on using MSCs are exploring the use of MSCs in hematopoietic cell transplantation (HCT), tissue healing (ex: articular cartilage), autoimmune diseases (AID) (ex: lupus, rheumatoid arthritis), and gene therapy vectors.

3.11.4.2.2.2.2.7 MSCs can be characterized by at least 3 phenotypic and functional minimal criteria: (a) their fibroblastic MSC-like morphology in culture, (b) their expression, or lack of expression, of a set of characteristic surface markers (eg, shown by flow cytometry), and (c) their multi-lineage differentiation into several characteristic mesenchymal lineages [22].

3.11.4.2.2.2.2.8 Safety of use: MSC therapeutics administered intravascularly can cause mild-to-more-severe adverse events most related to thromboembolic complications upon infusion of highly procoagulant tissue factor (TF/CD142)-expressing MSC products. As TF/CD142 expression varies widely depending on the source and manufacturing process of the MSC product, additional clinical cell product characterization (to these mentioned

above) along with clinical precautionary measures are needed to ensure the safe use of MSC products.

3.11.4.2.2.2.2.8.1 If cell products are intended for intravascular delivery, which is true for half of all clinical applications involving MSCs, the effects of MSC on coagulation and hemocompatibility must be assessed and expression of TF/CD142 shall be included as a phenotypic safety marker. This adjunct criterion will ensure both the identity of the MSCs as well as the safety of the MSCs has been vetted prior to intravascular delivery of MSC products.

3.11.4.2.2.2.2.8.2 As MSCs shifted from being primarily sourced from Bone Marrow (BM) to being increasingly sourced from non-hematopoietic tissues like adipose tissue (AT) and perinatal tissue (PT) sources[83, 84], the issue of hemocompatibility need to be anticipated:

3.11.4.2.2.2.2.8.2.1 Cells that are not routinely in contact with the blood commonly express variable amounts of highly procoagulant tissue factor (TF/CD142) [23,24] which can cause mild-to-severe thromboembolic adverse events upon intravascular infusion in patients without proper anticoagulation.

3.11.4.2.2.2.2.8.2.2 If MSCs are derived from perivascular cells or pericytes[22], then the expression of TF/CD142 would have the biological function to stop bleeding by initiating thrombosis in response to vascular injuries[22].

3.11.4.2.2.2.2.8.2.3 Importantly, clinicians and patients need to be properly informed, the risk for thromboembolic adverse events can be managed with appropriate treatment protocols, for example, the use of suitable anticoagulants such as heparin.

3.11.4.2.2.2.3 Tissue-specific progenitor cells:

3.11.4.2.2.2.3.1 Derived Tissue-specific progenitor cells are stem-like cells that reside within adult tissues.

3.11.4.2.2.2.3.2 Unlike embryonic stem cells, Tissue-specific progenitor cells are multipotent rather than pluripotent: i.e. are cells with a more restricted differentiation capacity: meaning they are generally restricted to generating the specialized cell types of their tissue of origin. normally produce a single cell type or a few cell types that are specific to that tissue (e.g. tenocytes, myocytes, astrocytes).

3.11.4.2.2.2.3.3 Tissue-specific progenitor cells are responsible for normal tissue renewal and turnover, such as neurons, intestines, skin, lung and muscle. stem/progenitor cells in bone marrow, neural progenitor cells in the brain, or mesenchymal progenitors in bone and cartilage).

3.11.4.2.2.2.3.4 Tissue-specific progenitor cells are under investigation for regenerative therapies in neurology, cardiology, and orthopedics.

3.11.4.2.2.2.4 Induced pluripotent stem cells (iPSCs), and/or their intermediate stages

3.11.4.2.2.2.4.1 iPSCs are artificially generated stem cells. They are reprogrammed from somatic adult cells such as skin fibroblasts. Increasingly iPSCs are being produced from different adult cell types.

3.11.4.2.2.2.4.2 IPSCs share many features of hESCs; they have self-renewing capacity, are pluripotent and form teratomas.

3.11.4.2.2.2.4.3 Their differentiation capacity seems to be dependent on the cell type and age of the cells from which the iPSCs were reprogrammed.

3.11.4.2.2.2.4.4 There is a knowledge gap to be addressed with respect to alterations of cell-specific / own regulatory pathways (i.e. cells own internal control system) ex: signaling pathways, transcription factors that regulate how cells behave when cells are taken out of their natural environment (e.g., cultured, expanded, reprogrammed). Changes will impact on how cells proliferate, differentiate, survive, and may have differences in gene expression and in epigenetic control). These characteristics may result in altered chimerism.

3.11.4.2.3 **Non-structural tissues:**

3.11.4.2.3.1 Non-structural tissues perform metabolic, immune, endocrine, or regulatory functions rather than providing physical support, protection, or movement, as seen in tissues like blood cells and nerve cells.

3.11.4.2.3.2 These tissues are often characterized by their biochemical roles, such as the metabolic functions of hematopoietic tissue or the signaling functions of peripheral nerves.

3.11.4.2.3.3 Examples include bone marrow, Nerve Tissues, Lymph nodes and other immune cells, pancreatic tissue and reproductive cells.

3.12 Classification of Human Cell Based / Tissue Based Therapies according to Manipulation

3.12.1 **Minimally manipulated (manipulation):**

3.12.1.1 **Minimally Manipulated Structural tissue:**

3.12.1.1.1 Structural Tissue undergone processing is considered minimally manipulated if that processing does not alter the original relevant characteristics of the tissue relating to the tissue's utility for reconstruction, repair, or replacement.

3.12.1.1.2 For stem cells recovered from processed structural tissues: if the recovered tissue through this processing lost its characteristics related to its utility for reconstruction, repair or replacement then the resulting stem cells are considered more than minimally manipulated.

Example: Stromal vascular fraction: Adipose tissue (structural tissue) recovered by tumescent liposuction then is subjected to processes (e.g., enzymatically digests, mechanically disrupts, etc.) to isolate cellular components (with or without subsequent cell culture or expansion). The adipose-derived stromal/stem cells would be considered as more than minimally manipulated cellular / nonstructural tissue as their characteristics were not maintained as it exists in the donor, prior to recovery and any processing that took place.

3.12.1.2 **Minimally Manipulated cells or nonstructural tissues:**

3.12.1.2.1 Cells or nonstructural tissues are considered minimally manipulated if the processing does not alter the relevant biological characteristics of cells or tissues.

3.12.1.2.2 Relevant biological characteristics of cells or nonstructural tissues generally include the properties of the cells or nonstructural tissues in the donor that contribute to the cells or tissue's function or functions. Examples of relevant biological characteristics of cells or nonstructural tissues include differentiation and activation state, proliferation potential, and metabolic activity.

Example: Relevant biological characteristics of hematopoietic stem/progenitor cells generally include the ability to repopulate the bone marrow by self-renewal and by differentiating along myeloid and lymphoid cell lines.

3.13 Classification of Human Cell Based / Tissue Based Therapies according to intended use (if homologous or not homologous)

3.13.1 **Homologous Use**

3.13.1.1 Homologous use refers to the repair, reconstruction, replacement, or supplementation of a recipient's cells or tissues with cells / tissues or cell / tissue-based products that perform the same basic function or functions in the recipient as in the donor, including when such cells or tissues are for autologous use.

3.13.1.2 Human cell based / tissues based medical product is for homologous use when it is used to repair, reconstruct, replace, or supplement:

3.13.1.2.1 Recipient cells or tissues that are identical (e.g., skin for skin) to the donor cells or tissues, and perform one or more of the same basic functions in the recipient as the cells or tissues performed in the donor; or,

3.13.1.2.2 Recipient cells or tissues that may not be identical to the donor's cells or tissues, but that perform one or more of the same basic functions in the recipient as the cells or tissues performed in the donor.

3.13.1.2.3 To meet the definition of homologous use, any of the basic functions that the human cell based / tissue-based medical product is expected to perform in the recipient must be a basic function that the source Human cell / tissue" performed in the donor.

3.13.1.3 A transplanted "Human cell based / tissue-based medical product" could replace missing tissue, or repair, reconstruct, or supplement tissue that is missing or damaged, either when placed in the same or different anatomic location, as long as it performs the same basic function(s) in the recipient as in the donor.

3.13.1.4 The basic functions of the following tissues / cells, for the sake of clarity, are as follows:

3.13.1.4.1 Hematopoietic stem/progenitor cells (HPCs) that are sourced from cord blood, peripheral blood, and bone marrow: Basic functions of HPCs include forming and replenishing the lymphohematopoietic system

3.13.1.4.2 Amniotic membrane: Basic function includes serving as a selective barrier for the movement of nutrients between the external and in utero environment, protecting the fetus from the surrounding maternal environment, and serving as a covering to enclose the fetus and retain fluid in utero.

3.13.1.4.3 Pericardium's basic functions include covering, protecting against infection, fixing the heart to the mediastinum, and providing lubrication to allow normal heart movement within chest.

3.13.1.4.4 Adipose tissue's basic functions include providing cushioning and support for other tissues, including the skin and internal organs, storing energy in the form of lipids, and insulating the body.

3.13.1.4.5 Skin's basic functions include covering, protecting the body from external force, and serving as a water-resistant barrier to pathogens or other damaging agents in the external environment. The dermis is the elastic connective tissue layer of the skin that covers, provides support and protects the body from mechanical stress.

3.13.1.4.6 Bone's basic functions of are supporting the body and protecting internal structures such as the brain.

3.13.1.4.7 Pancreatic islet's basic functions include regulating glucose homeostasis within the body.

3.13.2 **Non-Homologous Use**

3.13.2.1 If a human cell based / tissue based medical product is intended for use outside the original basic function as explained in the previous section would be considered non-homologous use

3.13.2.2 If a Human Cell / Tissue or Cell / Tissue based product is intended for use as an unproven treatment for a myriad of diseases or conditions, the Human Cell / Tissue or Cell / Tissue based product is likely not intended for homologous use only and will be considered and treated as human cell based / tissue based medical product for non-homologous use.

3.13.2.3 If the Human Cell based / Tissue based medical product is marketed for diseases/conditions unrelated to the tissue's natural function, it is considered as a non-homologous use.

3.14 Labeling, Promotion, Advertisement and Intent of the Clinics Impact on Classification

3.14.1 DoH determines the intent of the clinic or processing lab for minimally manipulated human cell based / tissue based medical product for homologous use by reviewing how the manufacturer / clinical program owner / and the administering clinic presents the product in its labeling, advertising, or other communications. To clarify:

3.14.1.1 **Minimally Manipulated Structural tissue:**

3.14.1.1.1 Structural Tissue undergone processing is considered minimally manipulated if that processing does not alter the original relevant characteristics of the tissue relating to the tissue's utility for reconstruction, repair, or replacement.

3.14.1.1.2 For stem cells recovered from processed structural tissues: if the recovered tissue through this processing lost its characteristics related to its utility for reconstruction, repair or replacement then the resulting stem cells are considered more than minimally manipulated.

3.14.2 The same applies when the intended use, as inferred from the surrounding circumstances under which the human cell based /tissue based medical product is offered, extends beyond homologous use — including situations where the product is promoted, provided, or otherwise made available for a purpose not reflected in its labeling or advertising.

3.15 Quality of Cell based Tissue based Therapies:

Quality shall be proven across the full life cycle of the Cell based /Tissue based Therapies starting by acquiring and collection of the starting material / human biospecimen, processing, cryopreservation / biobanking up to administration covering the three primary functions involved; the Clinical Program, Collection Facility, and Processing Facility.

3.15.1 **Collection of Facilities**

3.15.1.1 Collection facilities are facilities performing the role of collecting the bio-samples (as the starting source for cell based / tissue based therapies from patients / donors), there activity could go beyond collection until certain degree, they can be part of healthcare facility or part of the processing facility or part of the treatment facility, however the biospecimen collection facility

need to be DoH licensed as a service under the healthcare facility or as a standalone facility.

3.15.1.2 Collection facilities need to ensure the following measures are taken:

3.15.1.2.1 Holds an active DoH License as a collection facility, the license will specify the type of Human Bio-Samples collected: (Ex: Bone Marrow, Cord Blood, perinatal tissues, Blood, Adipose Tissue, cornea, etc.)

3.15.1.2.2 Get DoH documented approval for bio-samples acceptance criteria.

3.15.1.2.3 Instruments throughout the facility to be qualified and calibrated as applicable.

3.15.1.2.4 Have an effective quality management & quality assurance system in place for biospecimens and associated data resources, that covers every step from the collection, processing, processing, handling, storage, transfer, destruction and access, complying with quality standards and privacy regulations.

3.15.1.3 The QMS shall ensure documentation and traceability with special consideration for the following areas:

3.15.1.3.1 Measures for ensuring collection of acceptable quality samples and donor eligibility are in place and traceable across the full life cycle of the therapy (down to donor level and allow traceability up to the therapy receiving patient and therapy administering clinic).

3.15.1.3.2 The procedures for processing, including in-process quality controls, are consistently followed and recorded as per the documented standard operating procedures.

3.15.1.3.3 Good Documentation Practice and Data integrity is well embedded in the operating and recording systems: relevant instrument's logbooks and records reflecting the steps taken and tests including keeping the associated raw data per sample is key for enabling audits and proving compliance.

3.15.1.3.4 Documenting the Facility's compliance with the quality testing procedures as per the documented DoH approved acceptance criteria for all the collected bio samples.

3.15.1.3.5 Cryopreservation / biobanking / transportation:

3.15.1.3.5.1 Instruments used in Cryopreservation, as well as transportation vehicles including the containers holding the bio samples, must be qualified. Instruments, containers used for transporting the bio-samples (whether in crude status or processed are considered "qualified" if they meet regulatory standards for temperature control (maintaining -80°C for frozen biospecimens or 2–8°C for refrigerated samples) and include continuous temperature monitoring and alarm systems.

3.15.1.3.5.2 Preservation and biobanking conditions and timeframes must be validated to ensure the integrity and

viability of collected biospecimens. "Validated" conditions mean there is documented evidence that the specimens remain suitable for intended analysis or clinical use within the specified storage durations (e.g., up to 24 months at -80°C for certain tissues).

3.15.1.3.5.3 Transportation conditions and timeframes must also be validated up to the point of delivery, including transfer to a third-party processing facility or directly to clinical administration, as applicable. This validation shall specify acceptable temperature ranges (such as not exceeding 2–8°C for refrigerated shipments or remaining below -150°C for cryogenic transport) and maximum transport durations (for example, within 24–48 hours for fresh samples).

- Measures for full prevention of transmission of communicable disease are taken and documented.

3.15.1.4 Donor Eligibility Determination:

3.15.1.4.1 Human cell / Tissue collection establishments must screen and test donors for risk factors for, and clinical evidence of, relevant communicable disease agents and diseases and communicable disease risks associated with the transplantation.

3.15.1.4.2 Procedures for all steps that the collection facility performs in testing, screening, and determining donor eligibility must be established, and maintained.

3.15.1.4.3 Donor eligibility determination must be based upon the results of donor screening in and donor testing guided by the provided table 6 below.

3.15.1.4.4 Certain records must be always maintained at the collection facility once a donor eligibility determination has been made: These include a summary of records used to make the donor eligibility determination.

3.15.1.4.5 Until completion of the donor eligibility determination, collected / processed cell / Tissue / Cell / Tissue based product must be kept in quarantine, and clearly identified as quarantined to prevent improper release and distribution.

Table 6: HLA typing requirements per category of transplantations (cells, conventional nonengineered tissue, engineered tissue)

Category	Matching Donor Requirements	Role of HLA Typing	Notes / Examples
Hematopoietic Stem Cell Transplantation (HSCT)	- Requires **close HLA match** (8/8 or 10/10 allele-level). - Best donors: matched siblings or registry donors.	**Critical** – defines donor suitability and reduces risk of graft rejection & GVHD.	Bone marrow, peripheral blood stem cells, cord blood.
Conventional nonengineered Tissue Transplantation (cornea, skin, bone, cartilage, heart valves)	- **ABO blood type compatibility** is important. Donor screening for infectious disease. - HLA matching is usually *not strict*, except in some skin/cornea cases.	**Variable:** - Cornea: limited benefit. - Skin (permanent grafts): helpful but not always feasible. - Bone/valves/cartilage: often irrelevant due to decellularization/processing.	Corneal grafts, burn skin grafts, orthopedic bone/tendon grafts, cardiac valves.
Engineered / Regenerative Tissues (lab-grown, scaffold-based, iPSC-derived)	- If **autologous** (patient's own cells): **no donor matching needed**. - If **allogeneic**: donor matching less critical if tissue is decellularized or scaffold-based.	**Minimal to none:** - Autologous grafts: not needed. - Allogeneic engineered tissues: may still use partial HLA match or gene-edited universal cells.	Engineered skin, trachea, cartilage, vascular grafts, stem-cell derived organoids.

3.15.2 **Processing facilities:**

3.15.2.1 Any of the Facilities that will carry any processing steps on the collected cells / tissues up to the final Cell based / Tissue based therapy -to be administered to patients -must obtain a license from DoH if located in Abu Dhabi or need to be listed by DoH if located outside Abu Dhabi as a processing facility providing processing services to a "clinical program owner" in Abu Dabi-specifying the following:

3.15.2.1.1 The Processing Procedures approved for the facility.

3.15.2.1.2 In Process quality controls and release specs for the outcome whether unfinished or finished final therapy before handling to another processing facility / or clinic.

3.15.2.1.3 If any steps of testing or processing happen in third parties, these third party facilities need to be licensed / listed by DoH for the activity/ service they are providing and submit technical contracts in place defining the responsibilities of each party.

3.15.2.2 For contracted facilities based outside Abu Dhabi: in such a case listing at DoH is applicable rather than licensing:

3.15.2.2.1 Will include submitting documents proving same level of compliance required for the facilities in Abu Dhabi Emirate.

3.15.2.2.2 The listing application will be submitted by the relevant applicant who could be one of the following as applicable:

3.15.2.2.2.1 The processing facility in Abu Dhabi is contracting these facilities for certain steps in processing or testing for certain processed cell based / tissue-based outcome or therapy.

3.15.2.2.2.2 The clinical program owner of the therapy.

3.15.2.2.2.3 The therapy developer (Marketing authorization Holder)

3.15.2.3 Good Practices GXP: Processing facility needs to respect the following guidance documents / resources and get the relevant accreditation as stipulated in the relevant standard(s) issued by the DoH for Licensing the human bio sample collection / processing facilities. Mainly these facilities need to comply with:

3.15.2.3.1 The standards and requirements included for licensing Human Cells, Tissues, and Cellular and Tissue-Based Products' collection and or processing facility.

3.15.2.3.2 Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products

3.15.2.3.3 Current Good Tissue / Biobanking Practice for Human Cell, Tissue, and Cellular and Tissue-Based Product Establishments as per the Pan Human Biobank Standard issued by DoH, confirmed by periodic inspections and evidenced by accreditation from international organizations such as FACT.

3.15.2.4 Processing facilities are required to have an effective quality management and quality assurance system in place, documented and ensured traceability across all steps the bio-samples go through in the facility, with special attention to the following areas:

3.15.2.4.1 Processing procedures are validated for consistency and reliability for producing same approved outcome (whether intermediate therapy product before transferring it to another facility for further processing, or if in its finished product form to a clinic for administering to the intended patient.

3.15.2.4.2 Processing controls to prevent contamination that could result in an unsafe or ineffective product are in place.

3.15.2.4.3 Measures are in place to preserve integrity and function so that the products will work as they are intended.

3.15.2.5 Characterization and testing:

3.15.2.5.1 The facility is required to get DoH documented approval for the Characterization of the cells / Tissues and quality testing and final release criteria of the intermediate and finished therapy

3.15.2.5.2 Characterization and quality tests are validated if developed by the facility in Emirate of Abu Dhabi / verified if internationally developed and endorsed by international bodies for accuracy, sensitivity and reliability.

3.15.2.5.3 The facility needs to document its compliance with the DoH approved characterization, quality testing and release specs are met.

3.15.3 **Clinics / treatment facilities:**

3.15.3.1 Any Clinics must be licensed by DoH and accredited according to the specific class of the cellular- Tissue based products, each class will require its own licensing along with the list of the therapies provided by the clinic.

3.15.3.2 Clinics intending to administer cell-based or tissue-based therapies must first be listed as an authorized administration site for the specific therapy within a clinical program approved by the Department of Health (DoH).

3.15.3.3 Clinics shall comply with all the requirements stipulated in the approval of the therapy: such as but not limited to: Treatment protocol, eligibility criteria, Risk Management Plan, pharmacovigilance system, follow up measures, and follow up frequency and periods and others.

3.15.3.4 For every treatment that includes cells or tissues, regardless of the classification, clinics must obtain **documented patient informed consent**, which in addition to the core patient traceable information shall include:

3.15.3.4.1 A clear description of the procedure,

3.15.3.4.2 The claimed therapeutic intent,

3.15.3.4.3 Potential benefits and risks, including their likelihood/probability,

3.15.3.4.4 Available alternative treatment options, if any.

3.15.3.5 Clinics must ensure that safety measures are in place before, during, and after administration. These measures shall be tailored to the specific type of cells/tissues and aligned with both: a) this standard and b) applicable international disease-specific management guidelines.

3.15.3.6 Healthcare professionals involved in the administration of these therapies if clinicians or program administrators must be licensed and privileged by DoH and maintain specialized training and certification, demonstrate competence in handling and administering such products, and engage in continuous professional development as required by international standards (e.g., ISCT, ISSCR).

3.15.3.7 Clinics shall implement and comply with ethical oversight mechanisms, including institutional review boards (IRBs) or ethics committees, for therapies that are experimental, investigational, or used under compassionate/expanded access programs. Additionally, they need to get the right approvals in this regard from DoH.

3.15.3.8 Special attention shall be imposed on Human cells, tissues, and cellular and tissue-based products administered through higher-risk routes (such as intravenous injection, infusion, aerosol inhalation, intraocular injection, or central nervous system administration) and this category of the products will add additional layer for licensing / accreditation.

3.15.4 **Clinical Program for human cell-based / tissue-based therapies:**

3.15.4.1 The Clinical Program Owner, who develops cell- or tissue-based therapies, holds ultimate responsibility for their quality, safety, and efficacy, whether operating directly in Abu Dhabi or through an assigned representation of a DoH licensed clinic/s in Abu Dhabi.

3.15.4.2 The Clinical Program Owner (Sponsor in case of clinical trial framework) shall be the applicant to DoH for approving a specific cell based / tissue-based therapy regardless of its classification or its regulatory status (investigational / established authorized therapy).

3.15.4.3 Applications for clinical program: Prior to administering any cell or tissue-based therapy—regardless of its classification or type—clinics must obtain approval from the DoH according to the set procedures. In some cases, the application needs to be further approved by the national committee concerned and the EDE as applicable.

3.15.4.4 The DoH will grant its written approval to the eligible applications that meet all requirements. The DoH approval will specify: The accurate description of the therapy, the class and the proposed intended use, the follow-up plan and period and frequency of reporting to DoH along with the approved risk management plan in alignment with the Pharmaco-Vigilance (PV) good practices and PV standards issued by EDE and DoH.

3.15.4.5 Clinical program owner (Sponsors in case of investigational therapies) through the administering clinics/ Treatment Facilities are required to maintain registries incorporating a traceability system for therapy batches and patients, enabling the monitoring of clinical outcomes, the approved risk management plans (RMP) and pharmacovigilance data. They must systematically record and report adverse events, treatment results, and long-term follow-up data (up to 15 years) in accordance with international best practices (e.g., EMA ATMP guidance, WHO vigilance frameworks). Any exemptions shall be subject to the discretion of the DoH. DoH will oversee these registries and request periodic reports.

3.15.4.6 The Clinical Program Owner shall have access and ability to present the full file / documentation of the cell-based / tissue-based therapy that includes all details of the steps included in the therapy's full life cycle, including post administration surveillance (Pharmacovigilance and follow up to 15 years).

3.15.4.7 The Clinical Program Owner shall implement an insurance scheme designed to cover costs associated with potential program discontinuation or business exit.

3.15.4.8 If a clinical program owner intends to discontinue a cell- or tissue-based therapy or exit the business, they shall:

3.15.4.8.1 Notify DoH and get its written approval.

3.15.4.8.2 Must appoint another Abu Dhabi Emirate based and DoH Licensed facility to act as the new program owner. If this is not possible this needs to be discussed with the DoH-AD for appointing a program owner to follow up the cases where the therapy was administered

to and at the clinical program owner expense or under the coverage of the insurance scheme acquired for this purpose.

3.15.4.8.3 The new clinical program owner will be subject for the DoH evaluation and approval in the same way the original program owner was evaluated.

3.15.4.9 Program Owners and clinics shall ensure that they only engage with licensed and accredited facilities as stipulated in 5.1.4 below, and only within the scope of authorization relevant to the specific products being offered.

3.15.4.10 Program Owners and Clinics shall strictly comply with approved claims and stick to Homologous use for minimally manipulated cell and tissue-based products if not approved for other indications by DoH.

3.15.5 **Accreditation requirements for facilities involved in the full lifecycle of the cell-based / tissue-based therapies according to the role and the classification of the therapy:**

3.15.5.1 All facilities involved in any stage of the life cycle—from collection, manufacturing, and processing to administration (clinics) must be accredited as a facility or site.

3.15.5.2 If a site is responsible for only specific steps of the full cycle, such as providing a test as a third party, then it must either be accredited independently or be included in the clinical program or the site receiving the service. Noting, that both the sites and the contracted third party signed a technical contract providing all the details regarding the service provided and its specifics.

3.15.5.3 The accreditation for the sites involved in the lifecycle need be accredited and licensed as per following:

3.15.5.4 Foundation for the Accreditation of Cellular Therapy (FACT) as applicable to the level of manipulation and classification of the medical product as per following:

3.15.5.4.1 FACT: Common Standards for Cellular Therapies: These Standards represent the basic fundamentals of cellular therapy that can be applied to any cell source or therapeutic application and are intended to be used throughout product development and clinical trials. The Common Standards can be used to improve cellular therapy programs utilizing non-hematopoietic cells or treating non-hematological diseases.

3.15.5.4.2 FACT: International Standards for Hematopoietic Cellular Therapy Product Collection, Processing, and Administration[57]

3.15.5.4.3 FACT Standards for Immune Effector Cells: These Standards apply to immune effector cells used to modulate an immune response for therapeutic intent, such as dendritic cells, natural killer cells, T cells, and B cells. This includes chimeric antigen receptor T cells (CAR-T cells) and therapeutic vaccines. (Transplant programs that also administer immune effector cell programs should refer to the FACT-JACIE Hematopoietic Cell Therapy Standards for a complete

set of requirements pertaining to both HPC transplant and immune effector cells.)

3.15.5.4.4 FACT International Standards for Cord Blood Collection, Banking, and Release for Administration

3.15.5.5 In addition to the relevant health authority audit & certification: certificate of compliance with UAE / international Current Good Cellular or Good Tissue practice as applicable:

3.15.5.5.1 For UAE facilities according to the location: by the DoH for Abu Dhabi facilities and by the local competent authority / EDE for the rest of the Emirates as applicable by the UAE laws and regulations.

3.15.5.5.2 International facilities: By the concerned regulatory body at the Country of Origin.

3.16 Cell- based /Tissue- based Therapy Authorization as part of a clinical program licensing in Abu Dhabi Emirate according to the classification in terms of manipulation degree, intended use and risk level

3.16.1 **Minimally Manipulated Human Cell-Based / Tissue-Based Products therapies for Homologous use:**

3.16.1.1 Minimally Manipulated Human Cell-Based / Tissue-Based Products therapies for Homologous use needs to strictly meet all the following criteria:

3.16.1.1.1 Cells / tissues are Minimally Manipulated

3.16.1.1.2 Claim is only for Homologous use

3.16.1.1.3 Not combined with another article (with few exceptions like water, cryoprotectant).

3.16.1.1.4 Systemic effect: any of the two of the following shall be applicable:

3.16.1.1.4.1 The Human Cell / Tissue or Cell / Tissue based product does not have a systemic effect and is not dependent upon the metabolic activity of living cells for its primary function; or,

3.16.1.1.4.2 The human cell based / tissue based has a systemic effect or is dependent upon the metabolic activity of living cells for its primary function under a condition that it is for autologous use / for allogeneic use in a first- or second-degree blood relative, or for reproductive use.

3.16.1.2 Examples of Minimally Manipulated Human Cell-based, Tissues, and Cellular and Tissue-Based Products for homologous use include, but are not limited to,

3.16.1.2.1 bone, ligament, skin, dura mater, heart valve, cornea,

3.16.1.2.2 hematopoietic stem/progenitor cells derived from peripheral and cord blood

3.16.1.2.3manipulated autologous chondrocytes, epithelial cells on a synthetic matrix

3.16.1.2.4 Semen or other reproductive tissue.

3.16.1.3 Clinics in Abu Dhabi Emirate must obtain DoH explicit approval before offering any minimally manipulated cell-based or tissue-based therapies intended for homologous use (meaning therapies fulfilling the full conditions

for this category). Each therapy and its claims must be listed under the DoH licensed services of the clinic (Appendix 4 Application details).

3.16.1.4 For authorization by DoH, minimally manipulated cell-based or tissue therapy for homologous use must fulfill all the following requirements. Any exceptions must be highlighted and discussed with DoH. The requirements include:

3.16.1.4.1 The Clinical program Owners/ Sponsors along with all the facilities involved in any of the steps within the lifecycle of the Minimally Manipulated Human Cell based / Tissue -based therapy, need to be DoH licensed for that activity and get the relevant accreditation as stipulated in this standard (the relevant accreditation to be fulfilled within 2 years of the starting the first therapy). In case the cells-tissues are collected and or processed at different sites whether inside or outside Abu Dhabi, the following need to be provided:

3.16.1.4.1.1 The sites for collection and processing need to be clearly listed, each with address and role within the life cycle.

3.16.1.4.1.2 Signed Relationship letters with the applicant from each entity involved clarifying roles and responsibilities need to be provided.

3.16.1.4.1.3 Material transfer contracts need to be provided

3.16.1.4.1.4 Proof of accreditation for the service / activity provided issued to the relevant contracted site

3.16.1.4.2 Detailed Documentation to be provided to demonstrate the minimal manipulation: this will include the full Details of the source, collection and processing steps:

3.16.1.4.2.1 The collection: collection sites, donor eligibility criteria (if not autologous), collection process steps, the cells / tissues source (ex: blood, specific tissue, bone marrow, ….), the acceptance criteria.

3.16.1.4.2.2 Processing steps, including the Critical process parameters (CPP).

3.16.1.4.2.3 Safety precautions are applied as applicable per type of stem cell / tissue.

3.16.1.4.2.4 Final therapy/ Medical Product characterization and identifying the Critical Quality Attributes CQAs / release specs.

3.16.1.4.2.5 Potency Testing for the cell based medical products

3.16.1.4.3 Proof of homologous use: clear specification of intended use and rationale for claiming homologous use.

3.16.1.4.4 Pass the DoH Audits for compliance with the above

3.16.1.5 Minimally manipulated cell based/ tissue-based therapies authorized by DoH will be included within the list of therapies and medical products approved by

the DoH for that facility, with clear specifications/ details of the source cells / tissues, manipulation level, and intended Homologous use.

3.16.1.6 Out of scope: The following articles are not considered Minimally Manipulated Human Cell -Based / Tissue-Based Products for Homologous use accordingly must comply with the relevant regulatory requirements as stipulated in other sections of this standard or within the relevant standard as follows:

3.16.1.6.1 Vascularized human organs for transplantation: The Organ transplantation standards will apply

3.16.1.6.2 Whole Blood or full blood components or blood derivative products with minimal manipulation for non-homologous use are out of the scope of this section and will be discussed in the relevant sections within this standard, however for:

3.16.1.6.2.1 Whole Blood, and blood components minimally manipulated used for their basic function: Blood transfusion standard will apply,

3.16.1.6.2.2 For Blood components products used for out of basic function, then the relevant section in this standard will apply.

3.16.1.6.3 Secreted or extracted human products, such as milk, collagen, and cell factors, are out of scope of this section, except that semen is considered as Minimally Manipulated Human Cell-Based/ Tissue-Based Therapies.

3.16.1.6.4 Ancillary products used in the manufacture of Human Cell-Based / Tissue Based Therapies / Medical products.

3.16.1.6.5 Cells, tissues, and organs derived from animals other than humans (i.e. *Xenogeneic)*.

3.16.1.6.6 Platelet rich plasma (PRP, blood taken from an individual and given back to the same individual as platelet rich plasma) is not a Human Cell Based / Tissue -Based Therapy because it is a blood component product: the relevant part in this standard shall apply.

3.16.2 **Minimally Manipulated Human Cell-Based / Tissue-Based therapies for non-homologous use:**

3.16.2.1 Minimally Manipulated Human Cell-Based/ Tissue-Based Products for Non-Homologous Use need to meet all the Criteria for Minimally Manipulated Human Cell-Based / Tissue-Based Therapies for Homologous Use except for the systemic effect and claimed Homologous use.

3.16.2.2 All requirements for Quality for Minimally Manipulated Human Cell-Based / Tissue-Based Therapies for Homologous Use shall be applicable as well in here and complied with by the facilities involved in any step of their life cycle.

3.16.2.3 Additional requirements for claimed / promoted use Efficacy and Safety:

Clinical program owners or clinics offering minimally manipulated cell-based or tissue-based therapies for non-homologous use must apply for DoH authorization per therapy, application.

3.16.2.4 Therapies for non- homologous use will be categorized according to the following:

3.16.2.4.1 **Level one (Low risk):** Efficacy and Safety in relation to the claimed / promoted intended use need to be proven by a regulatory approval / authorization from a reference regulatory body for the same therapy with same specifications and process of production with a tech transfer agreement between the authorized company at the reference country and the representative clinical program owner in -Abu Dhabi.

3.16.2.4.2 **Level two: (Medium Risk):** If the Minimally Manipulated Human Cell-Based / Tissue-Based therapy for non-homologous use is authorized as an investigational new drug (IND), at a reference country. The DOH will decide about allowing its use under clinical trials framework and for the same phase of approval at the reference country, provided that:

3.16.2.4.2.1 The IND is manufactured by the same facility and has the same Marketing authorization holder/ sponsor company for UAE as in reference country where the IND approval was issues.

3.16.2.4.2.2 The IND specifications and testing requirements and intended use will be the same as the ones approved of at the reference country

3.16.2.4.2.3 “Unmet Medical Need” for the intended use of the IND provided the intended use of the IND wouldn’t pose the patients for risks beyond the expected benefit.

3.16.2.4.3 **Level Three A:** For Locally Developed Minimally Manipulated Human Cells in Abu Dhabi Emirate, Tissues, and Cellular and Tissue-Based Products for non-homologous use: The use of these products will be only allowed provided an approval from DoH is issued and on the following basis:

3.16.2.4.3.1 Submit a full CMC file (in line with the application (Appendix 4) to DoH to review and get early scientific advice for preclinical studies before allowing the product for clinical trials.

3.16.2.4.3.2 The Clinical Trials framework may be applied if:

3.16.2.4.3.2.1 The use addresses a medical/ aesthetic/ longevity needs where the scientific rational, published studies in peer reviewed journals, similar products approved internationally will conclude a profile that don’t pose risks to patients outweighing benefits.

3.16.2.4.3.2.2 Preclinical data / studies are carried under DoH oversight and demonstrates that benefits shown to outweigh risks.

3.16.2.4.3.2.3 Follow requirements of DoH standard for Human Biomedical Research.

3.16.2.4.3.3 After passing the clinical trial phases (1&2) successfully, full HTA is required by DoH for proceeding to clinical trial phase 3.

3.16.2.4.3.4 Registries as stipulated in the obligations of clinical program owner (sub-section 3.15.4.5) need to be fully complied with for both clinical trials phase and post authorization phase.

3.16.2.4.3.5 All the Involved facilities in the collection, processing and release of the product are internationally accredited by FACT as stipulated in (sub-section 3.15.5.4). If this is not possible and the HTA evaluation proved substantial benefits to patients, then an extended audit is required with a commitment to obtain the FACT accreditation before the full deployment of the product after an initial phase of clinical trials framework.

3.16.2.4.3.6 Special attention shall be imposed on Human cells, tissues, and cellular and tissue-based products administered through higher-risk routes (such as intravenous injection, infusion, aerosol inhalation, intraocular injection, or central nervous system administration)

3.16.2.4.4 **Level Three B: For internationally developed products that don't have a formal authorization for Human use from a reference regulatory body, the following conditions need to apply:**

3.16.2.4.4.1 To comply with all conditions for locally developed therapies in Abu Dhabi Emirate.

3.16.2.4.4.2 The intended/ claimed use address unmet medical need.

3.16.2.4.4.3 Full HTA evaluation by the DoH against the currently available options for the same claim if applicable.

3.16.2.4.4.4 An Abu Dhabi DoH Licensed Clinic for offering Minimally Manipulated Cell-Based / Tissue- Based therapies is assigned to represent the Developing Company as clinical program Owner.

3.16.2.4.4.5 The Developing Company and all parties (facilities) involved in the lifecycle of the therapy are licensed for the activities they are performing from their relevant Country of Origin (COO) regulatory authority.

3.16.3 **More than Minimally Manipulated Human Cell-Based/ Tissue-Based Therapies/ Medical** Products (out of scope of this Standard, applicants need to refer to the relevant standards to be published by DoH). These includes the Following Categories:

3.16.3.1 Advanced Cell therapies where human cells including Biobanked cells have undergone substantial processing beyond minimal manipulation using advanced techniques classified in here according to the Donor.

3.16.3.1.1 Autologous Use & Allogenic Use from identified matching Donor

3.16.3.1.2 Allogenic Use

3.16.3.2 Engineered tissues or tissue constructs intended for clinical application

3.16.3.3 Gene Therapies: Products involving gene editing or genetic modification of cells or tissues upon administration in Human: will be out of Scope of this standard.

3.17 Application Process for Minimally manipulated Human cell based / Tissue based therapies:

3.17.1 **Applicant:** for authorizing any Human Cell Based -Tissue Based, the applicant could be one of the following as applicable:

3.17.1.1 In case the therapy is developed and authorized out of UAE: The applicant would be the assigned DoH licensed clinic (to act as Clinical Program Owner in Abu Dhabi) by The Marketing Authorization Holder (Sponsoring Company). The assigned clinic needs to be licensed by DoH for administering Human cell-based -Tissue Based Therapies.

3.17.1.2 3.17.1.2 In case the therapy is developed in UAE: the applicant would be the developing entity (Rights Owner) in collaboration with the assigned Clinic for administration to act as Clinical Program Owner in Abu Dhabi. Additional clinics can administer the same therapy however the clinical program owner will add them to its program and keep the oversight on others and ensure compliance. DoH must approve every facility administering the therapy before they start the administration.

3.17.2 Preliminary classification & verification by DoH concerned Sector: This would be the first step in the application process, as is necessary to:

3.17.2.1 To determine whether there is any potential breach of intellectual property rights (IPR), the applicant must submit a clarification letter that includes all relevant patent information related to their therapy, processing, know-how and its intended use. Additionally, detailing the licenses/ authorization from the know how IP owners if any. In this letter, the applicant must confirm that no intellectual property rights are being infringed with respect to their therapy, its process, or intended use.

3.17.2.2 To determine the right regulatory pathway, it needs to be followed by the applicant.

3.17.2.3 The classification Decision will be issued by DoH to the applicant specifying the therapy class / type with guidance on the regulatory pathway. The classification letter wouldn't at any point be considered or promoted as approval of the therapy.

3.17.2.4 Applicants are required to refer to Appendix 3 for the minimum information to be provided for this step.

3.17.3 Full application must:

3.17.3.1 Be signed by both The MAH (Sponsor Company) and the Clinical Program Owner.

3.17.3.2 To attach copies from regulatory approvals if any

3.17.3.3 To attach a signed and notarized appointment letter to the clinic to act as the clinical program owner for that therapy

3.17.3.4 Full details of the therapy (including source of cells, manipulation/processing steps, etc. as per (Appendix 4).

3.17.3.5 for the facilities involved in the full lifecycle of the therapy: All relevant international accreditations and licenses including DoH licenses in Abu Dhabi need to be provided in the application. If not available the plan for the accreditation, licensing needs to be included.

3.17.4 Audit: All Abu Dhabi facilities will be audited for activities related to the therapy in the application. Facilities outside Abu Dhabi need to be accredited and licensed by a reference regulatory body as applicable.

3.17.5 HTA evaluation: if unmet medical need, therapies that are approved at non-reference countries would be subject for further evaluation for their added value in comparison to those available options, in this evaluation, cost effectiveness is one of the criteria provided a favorable risk benefit ratio is ruled out.

3.17.6 The outcome of the application assessment at DoH:

3.17.6.1 Full authorization: The authorized therapy will be listed under administering clinics mentioned in the application.

3.17.6.2 Authorization under clinical trial framework

3.17.6.3 Restricted / Conditional approval may be granted under controlled protocols with DoH strict oversight; if therapy meets its targeted outcomes as assessed by DoH, full authorization can follow. Clinical trial requirements compliance is critical for conditionally approved Human Cell-based/ tissue-based therapies, except these therapies may be provided for a fee.

3.17.7 Addition of clinics to the clinical program of the approved therapy: If the applicant wishes to add further clinics whether for collection or to administer same therapy; need to:

3.17.7.1 Submit a separate application for each clinic, specifying the role, attaching the relevant licenses as per the stipulated requirements above and in appendix 4.

3.17.7.2 Provide the technical agreements signed by both the concerned added clinic and the clinical program owner / Developing sponsor)

3.17.7.3 The added clinics need to pass the relevant audits.

3.17.8 Requirements for therapies approved for a clinical trial framework, or for restricted approval. The following requirements must be met before listing the therapy under the clinic's license concerned:

3.17.8.1 submission of an ethics committee approval,

3.17.8.2 completion of DoH's clinical trial approval

3.17.8.3 Adherence to DoH's regulations concerning Human biomedical research.

3.17.8.4 For conditional /restricted approval, shall comply with human biomedical research guidelines / standards issued by DoH except these therapies may be provided for a fee.

3.18 Compliance and Enforcement for Human Cell-Based/ Tissue-Based Therapies/ Medical Products:

3.18.1 All Human Cell-Based/ Tissue-Based Therapies/ Medical Products Provision in Abu Dhabi Facilities: would be subject to Approval and Monitoring by DoH, including their collection, processing /manufacture and clinical program.

3.18.2 Facilities involved in collection, Processing /Manufacturing and Clinics would be considered as breaching the laws and regulations of DoH AD if not fully comply with quality standards, for example but not limited to:

3.18.2.1 Inappropriate classification of the treatment by providing healthcare facility beyond the mandate of this standard could risk exposing patients to cross-contamination and inadequate characterization of the cell preparations, resulting in short and long-term risks for individual patients.

3.18.2.2 To source cells, cell-based & Tissue- Based therapies from non-qualified / non- licensed facility/ site by DoH, or from sites that were not declared in the application for allowing the cell-based / Tissue based therapy

3.18.2.3 Not complying with the processing steps and quality control measures stipulated in the authorization. In case of any change or variation these need to be reported to the department concerned at DoH and get written approval before implementation.

3.18.2.4 Not fully reporting or not complying with the steps that must be taken to prevent the introduction, transmission, and spread of communicable disease by the cell based / Tissue Based Therapies and their starting material (including donated biospecimens)

3.18.2.5 Promote / advertise cell-based / tissue-based therapies outside DoH authorized intended uses.

3.18.2.6 Claiming false ingredients that does not match reality.

3.18.3 The DoH will impose its enforcement activities against violating facilities and clinics offering unapproved Human Cell-Based/ Tissue Based Therapies, especially those using more than minimal manipulation or promoting products for nonhomologous uses.

3.18.3.1 DoH is particularly focused and will penalize facilities / healthcare practitioners or any person / entity involved in breaches in relation to:

3.18.3.1.1 Therapies that present the greatest safety risks, such as those administered systemically (e.g., via intravenous injection) or into sensitive areas like the central nervous system or eyes.

3.18.3.1.2 Products / therapies that are human cell-based / tissue based

intended to be used for the prevention or treatment of serious and/or life-threatening diseases and conditions: these are more likely to raise significant safety concerns than Human Cell-Based/ Tissue based therapies/ Products intended for homologous use because there is less basis on which to predict the product's behavior in the recipient, and use of these unapproved products may cause users to delay or discontinue medical treatments that have been found safe and effective based on robust evidence and approvals by recognized regulatory authorities.

Part 3: Subcellular Components

3.19 Exosomes:

3.19.1 Introduction- Extracellular vesicles (EVs) (generally referred to as Exosomes) have emerged as promising technology for diagnostic and therapeutic applications in clinical settings over the past decade[25]. The regulatory review requirements of EVs is still evolving. The development of standardized production protocols, establishing a clear understanding of the therapeutic mechanisms, and clarifying regulatory requirements are key for ensuring this important group of promising therapies attain their full potential and find their way to patients[26,27.] In this regard, DoH is adopting a risk-based classification framework to categorize Exosomes' products depending on source and claims as a rational approach.

3.19.2 Exosomes Definition and function in human body

3.19.2.1 Exosomes are nanosized extracellular vesicles (typically 30–150 nm) secreted by most cell types. Extracellular vesicles (EVs) are a diverse group of membrane bound structures originate from the endosomal compartment (multivesicular bodies) and are released into the extracellular space when these bodies fuse with the plasma membrane.

3.19.2.2 The generic name "EV" encompasses particles of various types secreted by cells, including EVs, micro vesicles (MVs)/ ectosomes, microparticles, apoptotic bodies (ABs), and small, medium, and large vesicles. The fusion of various EVs produces endosomes that develop into multivesicular bodies (MVBs) [25.]

3.19.2.3 EVs cannot replicate25 and are considered as subcellular structures enclosed by a lipid bilayer that resembles the plasma membrane.

3.19.2.4 Exosomes / EVs are involved in cell-to-cell communication by transporting complex cargo, such as genetic material (e.g., microRNAs, mRNAs, RNA, DNA), lipids, proteins. The cargo is selectively taken up by local and distant recipient cells and influences various cellular processes (e.g., gene expression, cell-to-cell signaling, immune response, tissue repair

3.20 Sourcing EVs:

3.20.1 Exosomes sourced from Humans

3.20.1.1 Cells and tissues (e.g., adipose tissue, umbilical cord, placenta, bone marrow)

3.20.1.2 Body fluids (e.g., blood, saliva, urine, milk, amniotic fluids, etc.)

3.20.2 Exosomes sourced from Animals (Mammals / Non-mammals)

3.20.3 Exosomes sourced from Nonconventional sources (nonhuman/nonmammal)

3.20.3.1 Animal products (e.g., honey, venom)

3.20.3.2 Plants (e.g., fruits, seeds, pollen)

3.20.3.3 Bacteria, fungus, parasite

3.21 Characterization of Exosomes [29,25]:

3.21.1 EVs consist of a lipid bilayer abundant in unsaturated fatty acids, phosphatidylserine, polyglycerol, sphingomyelin, cholesterol, and gangliosides. The lipid bilayer of EVs provides structural strength, stiffness, and a rigid environment that serves as a barrier to prevent enzymatic degradation, allowing for greater stability as a carrier molecule.

3.21.2 EVs are distinctly characterized by the presence of endosomal components, including specific bio markers like CD63, CD9, and CD81, and a variety of proteins, such as transcription factors and oncogenic regulators [7]. The protein composition of EVs serves as a reliable indicator of their subtype, providing insights into their biogenesis, release mechanisms, and cellular origin.

3.21.3 Specific proteins are typically present in EVs, regardless of their source, including heat shock proteins (HSP84, HSC70, and HSP90β), tumor susceptibility gene 101 (TSG101), and Alix.

3.21.4 The density of EVs typically falls within the range of 1.08 to 1.22g/Ml29,25 .

3.21.5 EVs carry genetic material from their parental cells, such as microRNAs, long noncoding RNAs, and circular RNAs [29,25.]

3.22 Naïve EVs:

3.22.1 All cell types can secrete EVs, which originate from the endocytic compartment of the producing cell and are subsequently secreted into bodily fluids. Thus, EVs can be collected and purified from bodily fluids or the extracellular environment.

3.22.2 Various pharmaceutical-grade, naïve extracellular vesicles are in early-stage clinical development

3.23 Synthetic /Engineered EVs

3.23.1 Synthesized EVs contain more lipids, including cholesterol, phosphatidylserine, and sphingomyelin, and less lysophosphatidic (bis)phosphatidic acid and phosphatidylcholine[57.]

3.23.2 EVs can undergo engineering either before or after production to incorporate native or synthetic molecules, thereby enhancing their specific targeting or therapeutic properties.

3.23.3 A range of engineered methods can be employed to introduce specific cargo into EVs. These approaches are categorized into two main strategies based on the timing of content addition: endogenous and exogenous loading[30.]

3.23.3.1 Endogenous loading:

Occurs at the cellular level, utilizing parent cells to incorporate therapeutic molecules into EVs during biogenesis. Techniques such as transfection, co incubation, physical

treatment are used to modify parent cells, enabling the packaging of desired cargoes into EVs as they form.

3.23.3.1.1 Co-incubation: Specifically, EVs can be packaged through co-incubation, enabling the diffusion of cargo across both cellular and EV membranes. However, Co-incubation often affords limited yields and variable loading efficiencies, posing challenges for large-scale applications.

3.23.3.1.2 Transfection: Desired nucleic acids can be loaded into EVs via transfection-based strategies.

3.23.3.1.3 Physical Treatment: Cargoes can also be loaded directly into EVs by physical treatment. Electroporation, sonication, and surfactant treatment create pores in the EV membrane to facilitate cargo loading.

3.23.3.2 Exogenous loading:

3.23.3.2.1 Involves directly introducing cargo into pre-isolated EVs through methods such as co incubation, ultrasonic treatment, electroporation, and specialized EV transfection kits[25] .

3.23.3.2.2 Exogenous techniques offer greater convenience and control over cargo loading, making these approaches popular in developing novel delivery systems.

3.23.3.2.3 Notably, transfection kits have gained widespread use because of their simplicity, speed, and high loading efficiency.

3.23.3.2.4 In situ assembly and synthesis: in this process, nanoparticles or biomolecules self-assemble into functional nanostructures within or on exosomes, either inside cells or in the extracellular environment, to form advanced drug delivery or diagnostic systems. These engineered exosomes can then be utilized for targeted cancer diagnosis, drug delivery, and therapy, leveraging the natural properties of exosomes to reach and act upon diseased cells. In short this facilitates the loading of metal nanoparticles by reducing metal ions to nanoparticles within the EV. Additionally, exosomes carrying the in-situ bio-self-assembled DNA–Au nanostructures could be an outstanding delivery system for dye-free targeted cancer detection and therapy.

3.23.4 Challenges with Engineering methods: Despite the diversity of engineering methods and their promised therapeutic advantages, the EV engineering process reliability is poorer than that of other artificially engineered nanovesicles (ex. Artificially engineered Liposomes) 25. The following challenges are not exhaustive, and any identified challenge need to be considered when assessing an Exosome Product

3.23.4.1 The yield is severely limited and of high cost: The limited ability of cells to secrete various EVs, the high difficulty and cost of large-scale cell culturing, and the time consuming and inefficient methods of EV isolation and purification. These drawbacks significantly hamper the industrial production of EVs[25] .

3.23.4.2 EVs have limited cargo loading efficiency: EVs are inherently packaged with natural proteins and nucleic acids that significantly increase the difficulty of

loading the required cargo. Although several methods for designing EVs to increase loading capacity are there, the cargo loading efficiency of EVs remains significantly lower than that of unpackaged synthetic liposomes[25] .

3.23.4.3 Challenging quality control: EVs, even when produced by a single cell type, are highly heterogeneous. The lack of highly sensitive, high throughput analysis of low-copy-number nucleic acids and proteins in the single EV dimension hinders the separation of heterogeneous EV populations, thereby yielding heterogeneous samples. In addition, EVs may inherit unwanted macromolecules from their parental cells because an important function of EVs is to remove harmful or unwanted substances from cells[25] .

3.24 Clinical Promise of Exosomes:

3.24.1 EVs are gaining considerable interest because of their role in cell biology and potential applications in therapy and diagnostics. This cell-to-cell communication supports a wide range of biological functions in both healthy and diseased states and offers the opportunity to develop new drug delivery systems.

3.24.2 EVs are distinguished by their lack of immune rejection and malignancy risk, stability, long-term maintenance, and ability to cross biological barriers. These attributes open up novel therapeutic strategies for treating various diseases[25] .

3.24.3 EVs hold significant potential in various medical applications, including:

3.24.3.1 Serving as biomarkers for disease diagnosis

3.24.3.2 Acting as drug delivery vehicles or therapeutic agents: studies have shown that natural and bioengineered EVs loaded with drugs can successfully penetrate the Blood Brain Barrier and cross the maternal placental barrier moreover remain stable in peripheral circulation. Their biocompatibility, ability to cross biological barriers, and potential for targeted delivery make EVs an innovative platform for advanced drug delivery systems. EVs are envisioned as excellent delivery platforms in biomedicine because of their low toxicity, minimal risk of an immune response, long in vivo circulation, nanoscale size for deep tissue penetration, multi-cargo loading capability, and surface molecular editing potential [29,25.]

3.24.3.3 functioning as immunomodulators to either stimulate or suppress the immune response: The capacity to isolate EVs from Mesenchymal stromal cells (MSC) cultures as a cell-free therapy that can circumvent immune rejection and tumorigenesis following injection represents a significant advantage and a comparatively safer treatment option[29,25 .]

3.24.3.4 Nevertheless, a more comprehensive understanding of the precise molecular pathways and biogenesis that give rise to the various subtypes of EVs is required to maximize the potential of EVs in clinical applications[25] .

3.24.3.5 Several companies focused on the production and commercialization of exosomes have begun clinical translation of extracellular vesicles such as therapeutics, as but not limited to respiratory failure from COVID19 treatment, for dystrophic epidermolysis bullosa and for diabetic foot ulcer. There are several active phase I/II clinical trials covering the mentioned examples.

3.25 Exosomes products require full regulatory assessment:

3.25.1 Full assessment means that the medical product/ therapy is fully assessed for quality, efficacy and safety by a thorough examination of its submission file, inspection and accreditation of its manufacturing / processing sites including collection sites.

3.25.2 Applicable to:

3.25.2.1 Exosome Products / therapies associated with Medical Claim/ longevity claim (see definitions), regardless of the dosage form or administering route.

3.25.2.2 Exosome Products / therapies administered to patients via parenteral route, by injection, or invasive procedure such as but not limited to micro needling or implants regardless of the claim associated.

3.25.3 Full regulatory assessment pathway means:

3.25.3.1 for internationally developed and manufactured:

3.25.3.1.1 to be fully assessed and authorized by reference regulatory authority and

3.25.3.1.1 authorized by EDE or Coded by Department of Health- if not authorized by EDE - applicable in the case of unmet medical need.

3.25.3.2 If locally developed and manufactured in Abu Dhabi Emirate: Exosome-based products that are locally developed and manufactured in Abu Dhabi Emirate intended for medical claims or for parenteral /injection or any invasive route of administration shall undergo a full regulatory assessment. Such assessment requires that the developer and/or manufacturer approach Department of Health for formal assessment from the earliest phases of development & formulation. DoH requires the Developers / manufacturers of Exosome products whether for medical claim or intended for injection / invasive route of administration to demonstrate that the product has been developed under the formal oversight of the DoH.

3.26 Oversight for locally developed and manufactured Exosome Product in Abu Dhabi

Oversight for locally developed and manufactured Exosome Product in Abu Dhabi Emirate shall extend to:

3.26.1 Manufacturing Process Development

3.26.1.1 The design, validation, and scale-up of the exosome isolation, purification, characterization, and formulation processes must be conducted under Good Manufacturing Practice (GMP) relevant to the stage and classification.

3.26.1.2 Raw materials, cell substrates, and excipients must be qualified and controlled according to internationally recognized standards.

3.26.2 Manufacturing site: Compliance with Good manufacturing Practice guidelines as per international standards. Specifically for Human / Animal derived exosome products:

3.26.2.1 EudraLex Volume 4 – EU Guidelines for Good Manufacturing Practice specifically for

3.26.2.1.1 Part IV: GMP for Advanced Therapy Medicinal Products (ATMPs): as it includes all important aspects such as but not limited to

traceability, donor eligibility (if human-derived), viral safety, potency assays.

3.26.2.1.2 Annex 2 (2018 update): Manufacture of Biological Active Substances and Medicinal Products for Human Use as it covers GMP for biologics, cell banks, and viral vectors.

3.26.2.2 Additionally, Biobank policies and standards issued by DoH need to be fully complied with.

3.26.3 Product Quality and Characterization: Comprehensive Chemistry, Manufacturing, and Controls (CMC) data presented in CTD format must be generated, Special attention to the following aspects:

3.26.3.1 Process validation for the full steps of production starting from isolation showing Consistency and reproducibility across batches.

3.26.3.2 Purification: (ultracentrifugation, filtration, chromatography):

A significant bottleneck in the process is the purification of EVs. Being small, low in density, and distributed widely throughout complex fluid environments, makes isolation a critical stage in manufacturing. The isolation process directly impacts the purity, yield, and overall production cost of EV-based therapeutics. Several purification and isolation innovative techniques leverage the unique physicochemical properties of EVs, such as density, mass, shape, charge, hydrodynamics, solubility, and surface features, to separate them from body fluids.

The applicants must specify the isolation techniques used (whether include differential centrifugation (DC), precipitation, size exclusion chromatography (SEC), ultrafiltration (UF), tangential flow filtration (TFF), and immunocapture) with a justification for its use and risk analysis (limitations containment plan).

3.26.3.3 Characterization:

3.26.3.3.1 Early-stage in vitro biological characterization and potency assessment best be conducted in conjunction with nonclinical in vivo studies.

3.26.3.3.2 Full characterization of exosome size, surface markers (CD9, CD63, CD81), contents, and purity.

3.26.3.3.3 Definition of critical quality attributes (CQAs) along with the assays for each.

3.26.3.3.4 Developers must establish validated assays for the characterization of exosomes, including size distribution, surface markers, cargo profiling, and release specifications. Refer to characterization section for more guidance.

3.26.3.3.5 In the development of EV therapeutics, the choice and thorough characterization of the EV source is equally important.

3.26.3.3.6 Evaluating EV formulations, identifying specific EV markers, and determining both purity and quantity—each representing unique

challenges that are integral to quality control and process parameter definition.

3.26.3.3.7 The developer shall justify its product's active substance characterization aspects, potency tests, stability tests and relate each of them to the mechanism of action and the intended use.

3.26.3.4 In process and release controls and testing: including but not limited to:

3.26.3.4.1 identity, purity, potency, stability, and batch consistency. These tests need to be validated and justified by relating them to the product's safety and efficacy for it intended use.

3.26.3.4.2 Sterility, endotoxin, mycoplasma, and viral safety testing for collected cell pools and for the final product.

3.26.3.5 Upscaling: The primary challenge in preparing extracellular vesicles (EVs) as carriers for various therapeutic cargoes lies in the upscaling of cell cultures while preserving cellular stability. Stem cell expansion is particularly difficult due to their natural tendency to differentiate into multiple cell types, which can result in the release of EV mixtures with unpredictable characteristics.

3.26.3.6 EV and EV Products storage protocols: must be carefully considered to guarantee product stability and therapeutic efficacy.

3.26.3.6.1 Key factors include storage temperature, buffer composition, and the choice of storage containers.

3.26.3.6.2 Siliconized vials are recommended to minimize EV adhesion and loss during both purification and storage.

3.26.3.6.3 Phosphate-buffered saline (PBS) is commonly used as the storage medium.

3.26.3.6.4 The most widely accepted method for preserving EV raw material characteristics is freezing at −80°C; however, storage at 4°C can cause EV damage and aggregation.

3.26.3.6.5 Despite its effectiveness, maintaining ultra-low temperatures for storage and transport poses logistical and cost challenges. Freeze-drying (lyophilization) has emerged as a promising alternative, as research indicates it does not significantly alter the size or quantity of MSC-derived EVs.

3.26.3.6.6 The use of cryoprotective sugars during lyophilization further helps maintain enzyme activity within the EVs, comparable to samples stored at −80°C. This approach may provide a cost-effective and practical solution for the long-term storage and transportation of EV-based therapeutics without compromising their efficacy.

3.26.4 Preclinical Evaluation shall address

3.26.4.1 Biodistribution and pharmacokinetics (how exosomes are taken up, cleared, and metabolized).

3.26.4.2 Safety (toxicology, immunogenicity, tumorigenicity, off-target effects) consistent with requirements for biological medicinal products. Preclinical studies' designs need to be discussed with DoH before and after commencement.

3.26.5 Clinical Evaluation:

3.26.5.1 Clinical trials (first in Human, phase 1-3) must be designed in accordance with Good Clinical Practice (GCP) and comply with DoH standards and guidance documents for Human Biomedical Research.

3.26.5.2 The clinical trial designs need to be discussed with DoH before and after commencement, endpoints aligned to the intended medical claims and appropriate safety measures are taken in consideration.

3.27 Regulatory Compliance with international standards:

3.27.1 EV / exosome medicinal products globally are not treated as separate review classification but are placed within the general biological drug review framework, according to their therapeutic properties, or along existing fast-track review pathways, depending on their therapeutic potential.

3.27.2 All products containing exosomes as their active substance falling under full assessment route as stipulated in this standard are required to concurrently comply with the regulatory requirements followed by reference regulatory authorities relevant to the medicinal product / therapy subclassification:

3.27.2.1 Biological product: In this case the medicinal product file follows the biological product CMC requirements set in the guidance documents provided by EMA and US FDA.

3.27.2.2 Gene therapy: some Exosome products are classified as Gene therapies, are still in the investigational phase. In this case the medicinal product file follows CMC requirements set in the guidance documents provided by EMA and US FDA for Gene therapies. Gene therapies are out of the scope of this standard.

3.27.2.3 If the Product is classified as a medical device as per the definition of medical device stipulated in pharmacy law no 38 for year 2024, then it is required to be fully assessed. It must undergo conformity assessment, clinical evaluation, and quality system audit by a Notified Body to obtain CE marking: Requirements include:

3.27.2.3.1 ISO 13485 manufacturing compliance.

3.27.2.3.2 Risk management (ISO 14971).

3.27.2.3.3 Clinical evidence (safety + performance).

3.27.2.3.4 Ongoing post-market surveillance.

Note: US FDA so far doesn't classify Exosome products as medical devices.

3.27.2.4 If the Exosome Product is for topical use and plant origin and has medical claim: need to follow the requirements for conventional medicinal products of new molecular entity. Note: So far there is no plant derived exosome product for topical use is classified / approved as medicinal product / medical device by reference regulatory authorities.

3.28 Ongoing Oversight for authorized Exosome products under full assessment route

3.28.1 Authorized Exosome products developers / sponsoring entity needs to ensure they comply with all regulatory post approval requirements

3.28.2 Post-market surveillance, pharmacovigilance, and risk management plans shall be established as conditions of authorization.

3.28.3 The developer/ authorized marketing authorization holder must maintain continuous quality oversight and report concerns to the DoH.

3.29 Application process to DoH for full assessment route

3.29.1 The applicant could be one of the following as applicable:
The product's distributor provided has a formal authorization from the international Marketing authorization Holder.

3.29.2 If locally developed in Abu Dhabi Emirate: The Abu Dhabi local Developer / manufacturer or the local Abu Dhabi owner of the product. Provided the relevant authorization letters and relationship letters are provided by all involved in the lifecycle of the product.

3.29.3 The clinic, in case not registered by EDE, however, has an internationally recognized approval. This option is kept for unmet medical needs. In this case the clinic needs to provide the distributor with details about who will import the product for their strict use.

3.29.4 Classification application to DoH concerned Sector is the first step. This step is required to define the product class, the regulatory pathway and requirements. Appendix 5 will provide the main information required to be provided by the applicant. Further information may be required by DoH in case needed. The classification decision will be issued by DoH to the applicant.

3.29.5 Full application process: After classification is completed, the applicant will provide the information as per the classification of the product and its place of manufacturing and development and as per requirements stipulated in the relevant sections above:

3.29.6 For products registered by EDE are only required to apply for coding.

3.29.7 For Products internationally developed and produced and authorized by a recognized reference regulatory authority, need to be evaluated fully by DoH, provided the product address an unmet medical need. In such a case, the applicant needs to comply with the coding process for un-registered products issued by DoH.

3.29.8 For Exosome products with medical claim and produced internationally however have regulatory approvals from non-reference country: These products need to:

3.29.9 Address unmet medical need

3.29.10 Pass an HTA evaluation comparing it for available options. If proven a substantial favorable profile or address unmet need then the applicant needs to:

3.29.11 Submit a full CTD file

3.29.12 The product and manufacturing sites involved in the lifecycle including collection sites to be fully evaluated as per the criteria stipulated for the Locally developed Products in sub-section 3.26.

3.29.13 Inspection may be required in case the product is not manufactured in a site that has reference country approval for its GMP and for the same line of the product in the application (Biologic, human derived products, etc.)

3.29.14 If the product successfully meets all the above evaluation criteria, it may be granted conditional authorization for use in Abu Dhabi clinics under a clinical trial framework for an initial phase, pending full regulatory approval. Such use shall be contingent upon full compliance with all applicable requirements of the Department of Health (DoH) Standards for Human Biomedical Research, including prior approval by a recognized Research Ethics Committee. All provisions shall apply with the exemption from providing the product to patients for free.

3.29.15 Acceptable Claims and Labeling for Exosomes products subject to the full assessment regulatory pathway:

3.29.16 Cosmetic and Health claims for exosome products are not acceptable substitutes for regulatory approval in therapeutic use.

3.29.17 For Exosome products qualified under the full assessment regulatory pathway: The clinics, pharmacies, marketers and developers must consistently comply with the authorized claims by DoH or by EDE for that product whether explicitly stated in any medium or implied from context.

3.30 Conduct and Enforcement

3.30.1 The applicant Advertisement, Processing, offering, advertising, and promoting exosome products that have not been authorized by EDE or the DoH to patients in Abu Dhabi constitutes a significant breach of both healthcare professional conduct and the law; this violation is regarded as particularly severe if the exosome product requires a full assessment pathway as per its definition in this standard.

3.30.2 Injectable exosome products / therapies, or exosome products / therapies administered via invasive methods such as microneedling, are strictly prohibited unless specifically authorized by DoH or EDE. These products must be administered exclusively in DoH licensed clinics provided that the DoH licensed services of that clinic are relevant to the approved claim / intended use of the product.

3.30.3 Products not registered by EDE regardless of their coding status by DoH are not allowed for any promotion or advertisement. These products must be provided by distributors to clinics solely on unsolicited basis.

3.30.4 Clinics or healthcare professionals deceiving patients with unsubstantiated claims about the potential for unapproved exosome products to prevent, treat or cure various diseases or conditions or claim that these products do not fall under the regulatory provisions for drugs and biological products – are violating the professional conduct and regulations of UAE.

3.30.5 As a general matter, exosomes used to treat diseases and conditions in humans are regulated as drugs and biological products and are subject to review and approval requirements as stipulated in this standard's relevant sections.

3.30.6 Health care professionals in Abu Dhabi shall report any adverse events related to exosome products or any other unapproved product to the DoH following the procedures set for Adverse Event Reporting issued by DoH. DoH in collaboration with other regulatory authorities monitors these reports and takes appropriate action necessary to ensure the safety of medical products in the marketplace.

3.30.7 Exosome Products classified as cosmetic or Health products

3.30.8 The Exosomes will fall under cosmetic class only if the exosomes containing finished products are offered for cosmetic or health claim only and meet the following conditions:

3.30.8.1 Administered either orally or topically

3.30.8.2 Plant origin.

3.30.8.3 If of bacterial origin: use through this route shall only be permissible provided that the bacterial material is fully inactivated (non-viable), and limited to non-living components or remnants (e.g., bacterial fragments or lysates). In such case additional clinical trials are needed to prove allergenic safety.

3.30.8.4 To be advertised / promoted only as dietary supplements, cosmetics, or delivery systems for nutraceuticals.

3.30.8.5 No disease or longevity claims

3.30.9 Requirements for Exosome Products classified as cosmetic or Health products to be allowed in circulation in Abu Dhabi:

3.30.9.1 If oral and marketed as “supports health” or of Health claim will be considered as dietary supplement and need to follow same regulatory requirements for dietary supplements in UAE.

3.30.9.2 If used in cosmetics (e.g., skin creams with “plant exosomes”) will be considered fall under cosmetic regulations, unless anti-aging/disease claims are made (then will be considered a medicinal product subject for full assessment regulatory pathway).

3.30.10 Artificially engineered nanovesicles (beyond exosomes):

3.30.10.1 In pharma/biotech, exosomes (naturally secreted nanovesicles) have inspired a whole family of artificially engineered nanovesicles for drug delivery, gene therapy, and regenerative medicine. Examples are Liposomes, Polymersomes, Micelles (lipid/polymeric), Nanodiscs, Niosomes, Artificial exosome mimics, Hybrid vesicles, Solid lipid nanoparticles (SLN/NLCs)

3.30.11 Liposomes containing medical products / therapies:

3.30.11.1 Definition: Liposomes are artificial, spherical vesicles made of one or more phospholipid bilayers surrounding an aqueous core. They are not living structures; they are engineered carriers that mimic cell membranes. Liposomes are widely used as drug delivery systems.

3.30.11.2 Sourcing: Liposomes are sourced via Synthetic routes by combining phospholipids and cholesterol. Liposomes size ranges from approximately 50 to 200 nm.

3.30.11.3 Regulatory classification: as per the reference regulatory authorities (FDA/EMA):

3.30.11.3.1 Liposomes is best classified as “Lipid-based nanocarrier / drug delivery systems” (nanocarriers) and not as medicines per se for the following reasons:

3.30.11.3.1.1 They are not active substances themselves (unless they contain an active drug). Example: liposomal doxorubicin, an FDA-approved oncology drug.

3.30.11.3.1.2 They are not considered “subcellular structures” because:

3.30.11.3.1.2.1 They are synthetic, not naturally occurring organelles.

3.30.11.3.1.2.2 They are not organelles (mitochondria, lysosomes, etc.).

3.30.11.3.1.2.3 They are not standalone “compounds” either — because they are mixtures/assemblies of phospholipids, cholesterol, and drug cargo.

3.30.11.3.2 Approvable uses for Liposomes:

3.30.11.3.2.1 Liposomes are used in nutraceuticals, health claim and longevity claim products to improve absorption of compounds (e.g., liposomal vitamin C, glutathione, NAD^+).

3.30.11.3.2.2 In the mentioned products above, liposomes, are marketed as delivery enhancers, not as bioactive agents themselves.

3.30.11.4 Conduct & enforcement: Accordingly, Liposomes per se are not allowed for promotion as active ingredients for any claim. If a product claims a liposome as an active ingredient, and intended use is medical or longevity claim, such products need proper regulatory approval pertaining to its classification. Such products will follow the full assessment route for exosomes.

3.30.12 Other Artificially engineered nanovesicles

Other Artificially engineered nanovesicles: there are other types of engineered nanovesicles, mainly classified as carriers and will follow same rules as liposomes. In here a non-exhaustive list of examples:

3.30.12.1 Polymersomes: Vesicles made from amphiphilic synthetic block copolymers (instead of natural lipids). Polymersomes are more stable than liposomes, have tunable permeability and longer circulation. Their use is still experimental as drug/gene delivery, nanomedicine.

3.30.12.2 Micelles (Polymeric or Lipid Micelles): are spherical aggregates of amphiphilic molecules, with hydrophobic core and hydrophilic shell. Manufactured using synthetic surfactants or block copolymers (e.g., PEG-PLA). Used for Solubilizing poorly soluble drugs, delivering hydrophobic molecules (e.g., paclitaxel micelles). Are classified as excipients and not active ingredients.

3.30.12.3 Nanodiscs are Planar lipid bilayer “patches” stabilized by scaffold proteins or polymers. Used for studying membrane proteins, delivering hydrophobic drugs, gene therapy. When used in medicinal product are classified as excipients and not active ingredients.

3.30.12.4 Niosomes are made from non-ionic surfactants and cholesterol, similar to liposomes but cheaper and more stable. Used in topical/transdermal delivery, cosmetics, experimental vaccines.

3.30.12.5 Polymersome-Derived Nanovesicles (Artificial Exosome Mimics) are Engineered nanovesicles mimicking exosomes, produced by extrusion of synthetic membranes or cell-membrane coatings. Used as experimental drug delivery, immune modulation, regenerative medicine. If the product containing Artificial Exosome Mimics has medical / longevity claim needs to follow the regulatory pathway of conventional medicinal products.

3.31 Mitochondria [23,31,24]

3.31.1 Mitochondria are organelles responsible for cellular energy production. Mitochondria contains a small amount of genetic material (DNA) that is separate from the DNA in the cell’s nucleus. The mitochondrial DNA is passed down only from mother to child and thus is inherited differently from the nuclear DNA.

3.31.2 There are no FDA-approved products that contain intact, functional mitochondria intended for general use. However, there are recently approved therapies for specific mitochondrial diseases and various dietary supplements that support mitochondrial function. These are out of scope and by definition the active moiety don’t fall under the subcellular structures or organelles definition.

3.31.3 Mitochondrial Replacement Technology (MRT) using donor mitochondria represents a possible treatment for mitochondrial disorders but introduces genetic modification and raises safety concerns.

3.31.4 The clinical use of MRT falls under medical products definition and will be treated as such. Accordingly, the MRT therapies will require full regulatory assessment and approval.

3.31.5 while some countries such as USA prohibits accepting applications for clinical research using MRT (clinical research using MRT in humans cannot legally proceed in the United States), DoH will carefully study these applications and will subject them for a thorough review and evaluation for ethical, scientific, safety and other aspects. in all instances, DoH maintains the authority to investigate and take enforcement action if it becomes aware of noncompliance in this regard whether:

3.31.6 Conducting unapproved research using/ affecting the Mitochondria

3.31.7 Offering unapproved treatments using/ effecting Mitochondria is taking place without proper approval from DoH.

3.31.8 Deviation from / incompliance with the proposed and approved protocols.

3.31.9 Advertising or promoting any research or treatment utilizing Mitochondria or Affecting it.

Part 4: Compounds

3.32 General Rules for Compounds

3.32.1 Scope of compounds covered in this part: Part 4 will address formulations comprised of specific ingredients, including the following multivitamins & trace elements, peptides, amino acids & nucleotides (collectively or individually referred to as compound(s)).

3.32.2 These preparations may contain one or more than one ingredient either from same type of compounds or combinations of ingredients from different types of compounds.

The compounds formulations could be either:

3.32.3 commercially readily available in finished pharmaceutical products or sourced from compounding pharmacies or compounding units at hospitals or against a prescription.

3.32.4 Clinics may advertise or provide compound preparations, often making longevity, medical, or health claims that lack evidence-based validation; accordingly, this section seeks to regulate these practices outlining the general rules and regulatory requirements clinics are required to observe and follow.

3.32.5 This chapter will address the above scenarios with a focus on formulations for administration to both patients and healthy individuals through routes intended to deliver the active ingredient directly into systemic circulation while bypassing the enteral (gastrointestinal) route and avoiding first-pass metabolism. Examples include parenteral preparations, intranasal sprays, inhalations, transdermal patches, or dispersible dosage forms, and other similar modalities.

The following general rules will be applicable to commercially available medical products containing any of the compounds:

3.32.6 Oral dosage forms or formulations that are intended for Enteral delivery route of administration: these will follow the same regulatory pathways for conventional medicinal products or dietary supplements as applicable and depending on the claim.

3.32.7 For health claims will follow dietary supplements regulations unless concentrations of compounds are beyond certain level as advised by regulatory authorities in UAE (i.e. EDE).

intended for Medical / longevity claims will necessitate:

3.32.8 A full regulatory assessment and approval by reference regulatory authorities and or EDE.

3.32.9 Those products approved not registered by EDE, however approved by international reference regulatory body and addressing an unmet medical need, would be allowed in Abu Dhabi only after complying with the unregistered products coding procedure and getting the coding approval from DoH.

Topical products, including creams, lotions, and other formulations with cosmetic claims and ingredients not intended for systemic absorption are allowed for circulation in Abu Dhabi and after complying with UAE cosmetic products regulation:

3.32.10 Allowable Claims for topical products classified as cosmetics are improving skin elasticity, boost collagen and hyaluronic acid production, providing deep hydration, brightening effects, skin anti-aging, skin firming, rejuvenating the skin, offering benefits like a more youthful glow and reducing wrinkles.

3.32.11 promoting skin / wound healing and other similar claims are considered as medical claims and will necessitate the product to follow same rules for oral dosage forms intended for medical claim or as medicated cosmetic according to the seriousness of the conditions treated (e.g. Nappy rash, and similar will be considered as medicated cosmetic).

3.32.12 In all instances products available commercially in finished product form above need to comply with the following requirements before allowing their circulation and use through Abu Dhabi be:

3.32.13 Registered with EDE or coded by DoH following the unregistered products route

3.32.14 imported and cleared via legal channels and sold by EDE licensed distributors to DoH licensed pharmacies.

3.32.15 They are only offered / prescribed for their associated approved health / medical claims as appropriate.

3.32.16 For compound(s) preparation prepared at compounding pharmacies: The following requirements need to be strictly complied with by clinics before offering, prescribing or / and administering in clinics in Abu Dhabi:

3.32.17 Clinics that offer or administer compounded preparations must adhere strictly to the requirements outlined in this entire section, as well as to any specific regulations applicable to each compound type.

3.32.18 The compound(s) preparation to be done in a DoH / EDE licensed compounding pharmacy with a valid Good Compounding Practice certificate for sterile injectables issued by EDE.

3.32.19 The compounding pharmacy to pass DoH inspection / verification or equivalent that is specific for the compound formulation and its line (sterile, aseptic filling, oral dosage form, etc).

3.32.20 Documentation and corresponding obligations of clinics offering, prescribing and or administering compound(s) formulations prepared at compounding pharmacies:

3.32.21 Prior to obtaining any preparations from a compounding pharmacy, clinics are required to establish a technical contract with the compounding pharmacy, signed by both parties. This contract must specify all technical requirements and conditions that the compounding pharmacy must fulfill in accordance with DoH's relevant standards, including this standard. Clinics must reserve the right to request documentation related to the sourced formulations from the compounding pharmacy, upon DoH's request. Failure of the compounding pharmacy to provide the necessary documentation for DoH's verification may result in a prohibition from conducting business with Abu Dhabi clinics. The clinic is required to ensure compliance of the compounding pharmacy with the sections below, and the relevant provisions in this standard per compound type.

3.32.22 Clinics are required to have a traceability system, where they record batch number of the preparation before administering to patients.

3.32.23 It is mandated that clinics request certificates of analysis, duly stamped or signed by the responsible pharmacist at the compounding pharmacy, for each batch of compounded formulation received. These certificates must be available for presentation to Department of Health inspectors upon request.

3.32.24 DoH will periodically verify the compliance of clinics in Abu Dhabi offering, prescribing or administering products prepared at compounding pharmacies via different routes such as audits, testing samples, verification of documents including contracts, invoices, certificates and other methods.

3.32.25 In case of doubt, clinics are required to facilitate DoH inspection process by requesting additional documents from the compounding pharmacies for DoH's verification.

3.32.26 The full formulation and process of preparation (SOP) shall be readily available to DOH's verification upon request. DoH understands that for Intellectual Property IP and other rights the documents could be provided either through administering clinics or directly from compounding pharmacies.

3.32.27 Clinics and pharmacies that fail to comply with these requirements or utilize banned, unlicensed / unqualified ingredients (ingredients imported from illegal channels), or materials sourced from unqualified suppliers (suppliers who are unqualified don't hold a valid GMP / license from a reference country) will be subject to suspension and financial penalties.

Active Ingredients sourcing and quality:

3.32.28 Bulk drug substances used in compounding may present significant safety risks if not sourced from trusted and qualified suppliers. Only substances eligible for compounding need to be used. In this regard, in general compounding pharmacies may only use bulk drug substances that

3.32.28.1 have a United States Pharmacopeia (USP) /European Pharmacopoeia (EP) monograph,

3.32.28.2 sourced from suppliers with GMP certification from reference regulatory authority and with certificates or proof that the substance is compatible with the monographs. In case of USA supplier, then the supplier shall be listed by USFDA for that active ingredient.

3.32.28.3 Are components of an approved drugs by reference regulatory authority if an applicable USP or EP monograph does not exist, or

3.32.28.4 appear on reference regulatory authority lists for active ingredients allowed for compounding (ex: FDA's 503A bulks list)[35,32] . if such a monograph does not exist and the substance is not a component of an FDA-approved drug product.

3.32.29 Use pharmaceutical-grade APIs with Certificates of Analysis (CoAs): covering identity impurities/counter-ions, sterility/bioburden, endotoxins, residual solvents, and water content.

3.32.30 Non-GMP, "research-use-only," or food-grade materials for injectables are strictly not allowed[35,36,37,32,33,34.]

3.32.31 Active ingredients must be imported by a EDE licensed distributor based on an import permit and clearance from EDE.

3.32.32 Aseptic preparation / Sterile formulations: the following are critical key standards to be followed by compounding pharmacies and need to be verified by the clinics in Abu Dhabi prescribing / administering compounded parenteral / injectable, inhalation or intranasal sprays compound (s) formulations:

3.32.33 Compounding must be strictly done under sterile compounding conditions following USP Chapter 797[35].

3.32.34 Microbiological & particulate safety tests (sterile formulations)

3.32.35 For every batch: Sterility testing is a must: apply USP <71> Sterility Tests as appropriate to the product and process validation strategy[39,36.]

3.32.36 For every batch Bacterial endotoxin testing is a must: meet limits using USP <85> (LAL/BET) and follow directions of US FDA on pyrogen/endotoxin testing[47,37.]

3.32.37 Particulate matter: comply with USP <788> for subvisible particles in injections (light-obscuration or microscopic methods)[50,38].

3.32.38 Stability, compatibility, and BUDs

3.32.38.1 Compounded preparation needs to be assigned for a beyond-use dates (BUDs) per USP <797> (2023) using sterility assurance level, container-closure integrity, compounding category, and stability/compatibility data[41,39]. conservative BUDs must be defined, unless robust stability data exist.

3.32.38.2 For multi-ingredient "cocktails," (example: multivitamin -TE preparations) the documentation of physicochemical compatibility (e.g.,

calcium/phosphate risks, precipitation, pH/osmolality for peripheral vs central administration) is a must.

3.32.38.3 Follow pharmacopeial/labeling limits for aluminum, preservatives, and infusion vehicles where applicable.[42,40].

Labeling:

3.32.39 Labeling shall include information for the diluent, the resultant strength, the container closure system, size / volume, BUD, batch number, production date, storage conditions and storage time. and provide patient/clinician information where mandated (e.g., risk of hypersensitivity with IV vitamins).

3.32.40 The Patient's name must be included, especially if the product is prescribed for patients' own use (ex.at home).

3.32.41 Labels must clearly state: The intended route of administration (oral or topical).

3.32.42 Labels shall include the disclaimer: "This product is not intended to diagnose, treat, cure, or prevent any disease."

3.32.43 Labels to include most important cautions: example; hypersensitivity for vitamins. If the direct label is not enough to include all cautions, then the label should refer patients & prescribers to associated materials or sources.

3.32.44 Claims, promotion, and patient protection

3.32.45 Unapproved/ unproven/ banned medicinal claims and COVID-related claims are strictly prohibited.

3.32.46 Unapproved/illegal supply chains for sourcing raw materials or finished products (e.g., peptides or GLP-1s labeled "research-only" but marketed for human use) are prohibited.

3.32.47 Advertising and promotion in general is not allowed for individual compounded products / formulations. Instead, clinics can:

3.32.48 advertise their services with general descriptions.

3.32.49 Promote their services and compounds to other clinicians without making any unsubstantiated claim.

3.32.50 Use of misleading terms describing compounded preparations in both advertisement / promotion such as "clinically proven," "safe injection," or "FDA-approved" "EDE approved" "DoH approved" is prohibited unless supported by formal authorization.

3.32.51 Adverse Event Reporting

3.32.52 Compounding pharmacies, distributors, and healthcare providers shall report serious adverse events associated with compounded preparations use as soon as possible and within 24 hours to the DoH.

3.32.53 High-risk compounded formulations, if authorized, shall include a Risk Management Plan (RMP) and periodic safety reporting.

3.33 Multivitamins (MV) and Trace Elements (TE):

3.33.1 Vitamins and trace elements (TEs) are required for specific metabolic functions. Vitamins are essential organic substances unable to be synthesized in the human body. TEs are minerals present at very low concentrations (equal to or less than 0.005% of body weight) in the human body.

3.33.2 Multivitamin and /or Trace Elements IV / parenteral administration involve administering a solution of vitamins, minerals, and other nutrients directly into the bloodstream to bypass digestion for faster and more efficient absorption.

3.33.3 While Multivitamin and / or TE (IV administration) popularly known as "Multivitamin Drips" are advertised by some clinics and promoted by compounding pharmacies for benefits like enhanced energy, boosted immunity, and improved appearance, it should be cautioned that scientific evidence for these benefits in healthy individuals is limited, and benefits are often no greater than oral supplements.

3.33.4 Clinics need to be aware and consider that routine IV multivitamin and / or TE administration for healthy adults without a clinical indication, carry risks (such as hypersensitivity, infection, thrombophlebitis, fluid/electrolyte errors, aluminum exposure, drug interactions).

3.33.5 Based on above and in alignment with the international regulatory authorities' position, DoH prohibit clinics, physicians or compounding pharmacies from offering or advertising Multivitamin and / or TE parenteral / invasive route administration for Healthy individuals in Abu Dhabi for unproven claims such as longevity, antiaging, immunity boosters and other similar claims. Several regulators and professional bodies have explicitly cautioned against casual use and unsupported claims; Multivitamin and or TE intended for parenteral administration are not recognized by the international regulatory authorities such as US FDA, UK MHRA and others for longevity or antiaging claims.

3.33.6 DoH reiterate that the use of Multivitamin and / or TE for parenteral / invasive route administration is restricted to on-label daily doses only. Clinics and Physicians in Abu Dhabi must not provide "mega-dosing" outside recommended daily doses for parenteral nutrition unless justified for a specific deficiency being identified41,42. In here the clinics need to refer to American Society for Parenteral and Enteral Nutrition (ASPEN), 2019, Link: Appropriate Dosing for Parenteral Nutrition: ASPEN Recommendations, PN-DosingASPEN.pdf [49,41] .

3.33.7 Clinics and prescribing physicians in Abu Dhabi should be aware of potential risks for Multivitamin and / or TE preparations for parenteral / invasive route administration and communicate these to the individuals seeking these treatments. Examples such as but not limited to:

3.33.8 Exceeding the daily doses and toxicity or Existing hypervitaminosis: High doses of certain vitamins and minerals have been linked to kidney damage, heart rhythm abnormalities, blood pressure changes, gastrointestinal symptoms and damage of the peripheral nerves. Hypervitaminosis A has been reported in patients with renal failure receiving 1.5 mg/day retinol and in patients with liver disease

3.33.9 Rare side effects could include trauma, bleeding or infection[49,43,41,42]

3.33.10 Hypersensitivity to any of the vitamins in the product

3.33.11 Allergy risk: many components of the multivitamin and or trace elements IV preparations whether active ingredients or excipients can cause allergies and avoidance is required with allergic patients: such as but not limited to thiamine can rarely cause severe reactions; some brands containing soy/peanut–derived excipients.

3.33.12 Renal function & aluminum load: Many parenteral products contain aluminum; toxicity is a particular concern in renal impairment.[49,43,44,41,42]

3.33.13 Hepatic disease / Vitamin A: Higher risk of hypervitaminosis A in liver disease or renal failure—avoid excess vitamin A and monitor.[49,43,44,41,42]

3.33.14 Drug interactions: Vitamin K antagonizes warfarin—monitor INR if the patient is anticoagulated (most adult MVIs contain ~150 µg K1).[49,43,44,41,42]

3.33.15 Interference with the diagnosis of megaloblastic anemia

3.33.16 Interference with urine glucose testing

3.33.17 Incompatibility with intravenous fat emulsions

3.33.18 Blood vitamin and TE concentrations should be periodically monitored in individuals getting these preparations on frequent basis to determine if deficiencies or excesses are developing.

3.33.19 Vitamin and or TE Drips need be infused slowly (≥10 min) under physician supervision and to be stopped if symptoms/ side effects appear[44,43]

3.33.20 Multivitamin and / or TE formulations for parenteral administration prepared at compounding units:

3.33.21 Prepare/administration of Vitamin and / or TE Drips must be restricted to UAE-licensed compounding pharmacies under proper sterile conditions to avoid infections/precipitates.

3.33.22 Compatibility/light-protection instructions need to be strictly followed (Vitamin A, D, riboflavin are light-sensitive).

3.33.23 Use of food-grade substances or substances intended for research use only in sterile or multivitamin/ TE preparations for parenteral routes is strictly prohibited.

3.33.24 Doses: follow dosing schedules at internationally recognized bodies for parenteral nutrition: acceptable references should be equivalent to American Society for Parenteral and Enteral Nutrition (ASPEN), 2019, Appropriate Dosing for Parenteral Nutrition: ASPEN Recommendations, PN-DosingASPEN.pdf[49,41]

3.33.25 Aluminum content to be Not more than 70 mcg/L for Adult Multiple Vitamins preparation. Aluminum may reach toxic levels with prolonged parenteral administration if kidney function is impaired, large amounts of calcium and phosphate solutions, which contain aluminum imply high risk of aluminum toxicity,

3.33.26 Zero preservatives are allowed in Vitamin and / or TE formulations sourced from compounding pharmacies.

3.34 Peptides

3.34.1 General provisions

3.34.1.1 Peptides refer to similar classes of compounds composed of chains of amino acids; Peptides -for the purpose of this standard- are synthetically derived peptides and are distinguished as different from proteins (i.e. biologics)[44]. DoH aligns with the US-FDA's definition for peptides and its classification as per the following:

3.34.1.2 Peptides are smaller compounds than proteins with equal or less than (≤) 40 amino acids and are regulated as drugs/ medicinal active pharmaceutical ingredient (API):in this regard only limited number of

peptides are allowed for formulations prepared at UAE licensed compounding pharmacies. Compounding pharmacies and clinics must avoid any banned peptide for human use.

3.34.1.3 Proteins are made of more than 40 amino acids per molecule and are regulated as biologics. Being classified as biologics, proteins are ineligible for compounding[44].

3.34.1.4 Some of peptides such as semaglutide (Ozempic) and tirzepatide (Mounjaro) are approved by reference countries for specific indications. However, many are banned from use by reference regulatory authorities such as US-FDA, mainly due to unproven effects, toxic impurities and dangerous side effects and other concerns linked to compounded treatments such as risk of variability between treatments / preparations, contamination risks, uncertified active ingredients and others.

3.34.2 **Banned Peptides**

3.34.2.1 Many popular peptides (e.g., BPC-157, others) are not permitted and/or sit in Category 2 ("significant safety risks") and therefore must not be prepared in compounding pharmacies for human use[32].

3.34.2.2 Appendix 2 lists the names of the banned peptides from incorporation in formulations prepared by compounding pharmacies under any circumstance.

3.34.2.3 In addition to the table provided in appendix 2 regarding banned peptides, the clinics need to ensure they get the most updated information on peptides with significant risks for compounding from international reference regulatory agencies such as US FDA.

3.34.2.4 Compounding pharmacies and healthcare providing facilities need to refer to the table in Appendix 2 and refrain from compounding / prescribing / administering the banned ingredients for Parenteral, inhalation or nasal spray administration routes.

3.34.3 **All commercially available peptides in finished pharmaceutical product form, regardless of dosage form, are required to:**

3.34.3.1 Adhere to the established regulatory procedures for conventional medicines as defined by EDE, ensuring that all products placed in UAE market receive authorization from EDE. Usage must be restricted to the approved indications specified in the authorization granted by the EDE.

3.34.3.2 If the product is not approved by EDE, however approved at a reference country for same marketing authorization holder, manufacturer (s), and product specifications, DoH may code this product provided it addresses unmet medical need and follows unregistered products coding pathway.

3.34.3.3 To be imported via legal channels by EDE licensed distributors and sold strictly at DoH licensed pharmacies.

3.34.3.4 Pharmacies that sell or clinics that prescribe and administer products containing peptides sourced from unauthorized channels will be considered in violation of Federal Pharmacy Law No. 38 of 2024 and may face significant penalties and sanctions.

3.34.3.5 The acquisition of peptides from unauthorized online sources is strictly prohibited, as such vendors often distribute unauthorized peptide injections manufactured from research-grade or non-pharmaceutical grade peptides, which are not approved for human use.

3.34.4 **Peptide formulations prepared at compounding units or pharmacies need to follow certain requirements:**

3.34.4.1 Only Subcutaneous and nasal sprays are allowed for preparation at compounding pharmacies, other parenteral formulations, inhalations or any other dosage form intended for direct systemic administration of peptides are prohibited.

3.34.4.2 Clinics in Abu Dhabi should consult DoH website or its concerned sections to get the most updated information on banned peptide formulations and suspicious sources.

3.34.4.3 Clinics shall ensure that they deal with licensed compounding pharmacies (EDE / DoH/ relevant health authority according to the location in UAE) and check various steps followed. The role of clinics in this regard will be further explained in the relevant sections pertaining to compounding requirements.

3.34.4.4 For Peptides: compounding pharmacies need to source peptides from certified / qualified suppliers (hold valid GMP and License from a reference Health Authority) provided their certificates of analysis covering the following aspects: sequence identity, counter-ion/salt form (e.g., acetate/TFA), peptide-related impurities and residual solvents; control sub-visible particles after reconstitution; validate diluents (bacteriostatic water compatibility). See table below.

Table 7: Attributes to be included in the CoA of peptide bulk substance.

Batch & Product Identification:	• Product name and description • Manufacturer's name and logo • Batch number and original manufacturer's batch details • Date of testing and manufacturing • Expiration date or retest date

Purity and Identity Testing:	• Purity: Typically confirmed by Reverse-Phase High-Performance Liquid Chromatography (RP-HPLC) or Ultra-Performance Liquid Chromatography (UPLC). • Identity: Verified by Mass Spectrometry (MS), confirming the peptide's molecular weight and sequence. Peptide mapping is also a key ID test, confirming the sequence of amino acids.
Impurities:	• Specified and unspecified impurities • Total impurities, with acceptable levels defined
Content	• Peptide content • Potency (if applicable, through bioassays)
Physical Characteristics:	• Appearance • Water content (e.g., by Karl Fischer titration)
Microbiology	• Endotoxin levels
If reconstituting lyophilized peptides/nucleotides, the diluents, container-closures, and compatibility (pH/osmolality, preservatives, adsorption) need to be qualified and well considered.[40]	

3.34.5 Glutathione (L-glutathione):

3.34.5.1 Glutathione is a thiol-tripeptide with a low molecular weight. It is produced in every cell in the body. Its principal role is to quench free radicals and maintain intracellular redox balance. It is important for detoxification and immune modulation as well.

3.34.5.2 As Glutathione has registered injectable products in UAE, accordingly, sourcing injectable Glutathione for IV administration from compounding pharmacies is prohibited as per the general rules governing compounding.

3.34.5.3 Registered, Glutathione parenteral products shall be only offered and prescribed for its approved labeled indications: used for severe liver disorders and for prevention of chemotherapy associated with neurotoxicity.

3.34.5.4 Intravenous administration of Glutathione for the purpose of skin whitening is strictly prohibited45,46including for registered Glutathione IV products. The primary concern associated with such administration is toxicity.

3.34.5.5 Injectable Glutathione formulations (other than IV injections) prepared at compounding pharmacies, are not allowed for prescribing based on its anti-melanogenic properties such as skin lightening and treatment of hyperpigmentation: patients seeking such treatments need to be informed of the limited evidence, the availability of oral and topical formulations of Glutathione and most importantly the potential toxicity from injectable formulations.

3.34.5.6 Advertising and promotion of glutathione in any dosage form for skin whitening is strictly prohibited.

3.35 Nucleotides (poly nucleotides)

Definition: Polynucleotides are polymers composed of long chains of nucleotides, which are the basic building blocks of DNA and RNA. They can be derived from natural sources like salmon sperm DNA or synthesized artificially.

3.35.1 NAD, NAD+ and NAD precursors

Definition:

3.35.1.1 NAD+ (Nicotinamide Adenine Dinucleotide) is a coenzyme found in all living cells. It plays a central role in energy metabolism, DNA repair, and cellular signaling — essentially acting as a molecular "currency" for energy transfer in the body. NAD^+ is the oxidized form of Nicotinamide Adenine Dinucleotide Hydrogen (NADH). Together they form a redox pair involved in transferring electrons in metabolic reactions.

3.35.1.2 NAD+ precursors are the "building block" molecules, such as nicotinic acid (niacin), nicotinamide (NAM), nicotinamide riboside (NR), and nicotinamide mononucleotide (NMN), that the body converts to produce nicotinamide adenine dinucleotide (NAD+)

3.35.2 NAD+ Production: The body synthesizes NAD^+ from dietary niacin (vitamin B_3) or its precursors — nicotinamide riboside (NR) and nicotinamide mononucleotide (NMN).

3.35.3 Functions of NAD^+ naturally biosynthesized in the human body:

3.35.3.1 NAD+ is essential for mitochondrial function and ATP production through glycolysis, the citric acid cycle, and oxidative phosphorylation. It acts as an electron carrier, converting between NAD^+ and NADH during these reactions.

3.35.3.2 NAD^+ activates sirtuins (SIRT1–7) — enzymes linked to DNA repair, anti-aging, and inflammation control. Decline in NAD^+ levels with age is associated with mitochondrial dysfunction and accelerated aging. NAD+ Influences glucose, lipid, and amino acid metabolism and helps regulate insulin sensitivity and lipid oxidation.

3.35.3.3 NAD+ also has role in cell protection as it supports the function of PARPs (poly ADP-ribose polymerases), which repair DNA damage.

3.35.3.4 NAD+ also is Involved in cell survival pathways and immune responses.

3.35.4 Nucleotides/NAD^+ sterile parenteral formulations claimed indications and international regulatory status

3.35.4.1 For NAD compounding pharmacies, healthcare providing facilities / clinics and Health Care professionals need to completely avoid unsubstantiated efficacy claims. [48]

3.35.4.2 Side effects and risks need to be communicated to patients; the most common associated with NAD's use are muscle pain, nervous disorders, fatigue, sleep disturbance, headaches

3.35.4.3 NAD^+ compounded formulations: it is important to note that so far there is no commercially available NAD^+ injection authorized by a reference regulatory authority.

3.35.5 NAD+ sterile injection compounding specific technical requirements:

3.35.5.1 Only suitable, pharmaceutical-grade ingredients of NAD must be used from certified suppliers[32,33]

3.35.5.2 Food-grade or research only bulk are strictly not allowed for sterile IV compounding of NAD.

3.35.5.3 Very tight controls on endotoxins and bioburdens need to be strictly observed, nucleotide preparations can be highly pyrogen prone.

3.36 Other Poly Nucleotides:

3.36.1 Other polynucleotides potential intended uses and Mechanism of Action:

3.36.1.1 Hydration: Polynucleotides have a high capacity for water retention, which helps in moisturizing and hydrating the skin.

3.36.1.2 Regeneration: They promote tissue regeneration and healing by providing a scaffold for cellular growth and by stimulating fibroblast activity.

3.36.1.3 Anti-inflammatory: Polynucleotides have anti-inflammatory properties, which can reduce redness and swelling in treated areas.

3.36.2 Other polynucleotides potential claims:

3.36.2.1 Cosmetic claims such as skin rejuvenation: claims like enhancing skin texture, elasticity, and hydration.

3.36.2.2 Medical claims:

3.36.2.2.1 Wound healing: Accelerating the healing process in damaged tissues.

3.36.2.2.1 Reducing the appearance of scars and fine lines.

3.36.2.3 Medical claims are not allowed for nucleotide products for topical use: such as promoting skin / wound healing and other medical claims.

3.36.3 Injectable Polynucleotides available in commercial finished product form: Noting that while polynucleotide treatments approved by the relevant regulatory authorities in Europe and Asia and are widely used in these countries, injectable polynucleotides are not yet approved by the U.S. Food and Drug Administration (FDA).

3.36.3.1 For injectable polynucleotides the following requirements need to be met before allowing for circulation in Abu Dhabi market or offered in Abu Dhabi clinics:

3.36.3.1.1 Need to be approved by a reference regulatory body and EDE or

3.36.3.1.2 The medical product needs to be authorized by a reference regulatory authority, its claim addressing an unmet medical need, and to be approved by DoH according to the DoH's set procedure for unregistered medical products.

3.36.3.1.3 Imported via an EDE licensed distributor and via a proper import permit from EDE.

3.36.3.2 EU requires polynucleotide injectable products for aesthetic claims to follow medical device class 3 requirements. Example:

Polydeoxyribonucleotide48` (PDRN) injectable made from DNA fragments derived from salmon, noting that the USA FDA didn't approve any PDRN injectable product yet and classified it as a biological product and is required to follow biological products requirements.

3.36.4 For injectable Nucleotides prepared at compounding pharmacies on small scale, the following requirements need to be strictly followed by the clinics and healthcare professionals offering compounded nucleotides / polynucleotide including NAD+

3.36.4.1 The active ingredients are not available in commercially finished products for same administration route.

3.36.4.2 Compounded preparation claims:

3.36.4.2.1 strictly not to be for medical / longevity claims. The claims shall be restricted to general well-being enhancement only.

3.36.4.2.2Side effects and risks need to be communicated to patients as available from literature and published peer review journals.

4. Key stakeholder Roles and Responsibilities

The following are the key stakeholders impacted and need to align / comply with this standard:

Stakeholder	Roles & Responsibilities
DoH Licensed Healthcare Providing facilities offering therapies or treatments with longevity / regenerative effects or therapies sourced from Human blood, cells, or Tissues regardless of the claim.	need to comply with the standard and get the required licenses, accreditations and approvals. Additionally need to contract only licensed third parties / source the therapies through legitimate channels.
Licensed Healthcare Professionals including physicians and Pharmacists	To comply with the standard
Processing facilities: facilities involved in processing or manufacturing any of the therapies within the scope of this standard	Need to comply with the standard and get the required licenses, accreditations and approvals.
Compounding Pharmacies	Need to comply with the standard and get the required licenses, accreditations and approvals.
Marketing Authorization Holders / developers of therapies or right owners for cell -based / tissue-based therapies	To ensure there are authorized representative clinical program owners in Abu Dhabi, ensure the long term follow up and the implementation of the approved Risk Management Plans in Abu Dhabi
Marketing Authorization Holders for the rest of the therapies within the scope of this standard	To comply with Pharmaco- Vigilance plans including collection and reporting of the Adverse Drug Events and ensure the implementation of the approved Risk Management Plans in Abu Dhabi
Research centers involved in regenerative medicine research	Need to get the required licenses, accreditations and approvals as per the standard has stipulated. Also need to approach the DoH for advice and guidance.

5. Monitoring and Evaluation

5.1 Facilities will be provided with a transition period of 6 months to finalize their corrective actions in relation to this updated version of this standard.

5.2 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.

5.3 DoH Audit will ensure compliance to this document after preparing a checklist generated based on this standard.

5.4 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.

5.5 The following are the key success factors along with relevant stakeholders aimed to be monitored and evaluated periodically and ensure continuous improvement to the healthcare ecosystem.

Key Success Factor	Stakeholder	Responsibility
% of healthcare facilities offering therapies with claims of longevity / regenerative effect Licensed by DoH, accredited in compliance with the standard	Healthcare Provider facilities (Clinics / Hospitals).	Facilities Inspection Section-DoH Facilities Licensing Section-DoH
% of locally (in Abu Dhabi Emirate) Developed Therapies with Longevity / regenerative effect Claims reviewed and provided oversight by DoH	Processing facilities / Research facilities/ Developers using Abu Dhabi Based facilities	Health Life Sciences Sector-DoH
% decrease in complaints from patients related to therapies with claims for longevity / Regenerative effects or within the scope of this standard.	Healthcare Provider facilities (Clinics / Hospitals). Healthcare Professionals	Health Life Sciences Sector-DoH
% of non-compliant Healthcare facilities with the standard out of all facilities licensed in Abu Dhabi Emirate	Healthcare Provider facilities (Clinics / Hospitals).	Facilities Inspection Section-DoH
% of non-compliant Healthcare facilities with the standard out of the total facilities licensed in Abu Dhabi Emirate for regenerative medicine / longevity/ provision of human cell-based / Tissue based services	Healthcare Provider facilities (Clinics / Hospitals).	Facilities Inspection Section-DoH

6. Enforcement and Sanctions

6.1 DoH can impose sanctions in relation to any breach of requirements under this standard in accordance with the Complaints, Investigations, Regulatory Action and Sanctions Policy, and the Healthcare Regulator Manual.

7. Relevant Reference Documents

No.	Ref. Date	Reference Name	Relation Explanation / Coding / Publication Link
1	2024	Regulating platelet-rich plasma (PRP), platelet-rich fibrin (PRF) and conditioned serum	https://www.tga.gov.au/resources/guidance/regulating-platelet-rich-plasma-prp-platelet-rich-fibri prf-and-conditioned-serum
2	2022	Platelet Rich Plasma and Its Use in Hair Regrowth: A Review. Drug Des Devel Ther.	https://pubmed.ncbi.nlm.nih.gov/35300222/
3.	2016	DEPA classification: a proposal for standardising PRP use and a retrospective application of available devices.	https://pubmed.ncbi.nlm.nih.gov/27900152/
4.	2015	A call for a standard classification system for future biologic research: The rationale for new PRP nomenclature.	https://pubmed.ncbi.nlm.nih.gov/25864661/
5.	2017	Contributions for classification of platelet rich plasma-proposal of a new classification: MARSPILL. Regen. Med.	https://pubmed.ncbi.nlm.nih.gov/28758836/
6.	2018	A review of platelet-rich plasma: history, biology, mechanism of action, and classification. Skin Appendage Disord.	https://pubmed.ncbi.nlm.nih.gov/29457008/
7.	2020	Platelet-rich plasma accelerates skin wound healing by promoting re-epithelialization. Burns Trauma.	https://pubmed.ncbi.nlm.nih.gov/32821743/
8.	2016	Platelet-rich plasma modulates actions on articular cartilage lubrication and regeneration. Tissue Eng Part B Rev.	https://pubmed.ncbi.nlm.nih.gov/27109909/
9	2025	The role of platelet-rich plasma in biomedicine: A comprehensive overview, iScience,	https://doi.org/10.1016/j.isci.2024.111705 https://www.sciencedirect.com/science/article/i/S2589004224029328

10	2025	WMDA | Matching Donors | Serving Patients	https://wmda.info/publications/
11	2024	Adverse events related to platelet-rich plasma therapy and future issues to be resolved.	https://doi.org/10.1016/j.reth.2024.07.004
12	2023	Efficacy and safety of platelet-rich plasma injections for the treatment of osteoarthritis: a systematic review and meta-analysis of randomized controlled trials.	https://pubmed.ncbi.nlm.nih.gov/37441691/
13	2021	Effect of Intra-articular Platelet-Rich Plasma vs Placebo Injection on Pain and Medial Tibial Cartilage Volume in Patients with Knee Osteoarthritis.	https://pubmed.ncbi.nlm.nih.gov/34812863/
14	2018	Platelet-Rich Plasma: Review of Current Literature on its Use for Tendon and Ligament Pathology.	https://pubmed.ncbi.nlm.nih.gov/30203334/
15	2025	Platelet-rich plasma injections as a second-line treatment in patients with tendinopathy-related chronic pain and failure of conservative treatment: a systematic review and meta-analysis,	https://doi.org/10.1093/pm/pnaf022
16	2023	Current Status and Advancements in Platelet-Rich Plasma Therapy.	https://pubmed.ncbi.nlm.nih.gov/38021947/
17	2023	Understanding Solid-Based Platelet-Rich Fibrin Matrices in Oral and Maxillofacial Surgery: An Integrative Review of the Critical Protocol Factors and Their Influence on the Final Product,	https://pubmed.ncbi.nlm.nih.gov/38003952/
18	2022	Platelet Rich Plasma in Gynecology-Discovering Undiscovered-Review	https://pubmed.ncbi.nlm.nih.gov/35564681/
19	2024	The value of intraovarian autologous platelet rich plasma in women with poor ovarian reserve or ovarian insufficiency: a systematic review and meta-analysis	https://bmcpregnancychildbirth.biomedcentral.com/articles/10.1186/s12884-024-06251-2
20	2018	EMA: Scientific recommendation on classification of advanced therapy medicinal products: autologous bone marrow-derived Mesenchymal cells suspension (18 days)	https://www.ema.europa.eu/en/documents/report/scientific-recommendation-classification-advanced-therapy-medicinal-products-autologous-bone-marrow-derived-mesenchymal-stem-cells_en.pdf

21	2021	Molecular characterization of hematopoietic stem cells after in vitro amplification on biomimetic 3D PDMS cell culture scaffolds.	https://doi.org/10.1038/s41598-021-00619-
22	2022	Improved MSC Minimal Criteria to Maximize Patient Safety: A Call to Embrace Tissue Factor and Hemocompatibility Assessment of MSC Products.	https://pubmed.ncbi.nlm.nih.gov/35641163/
23	2023	Potency Assurance for Cellular and Gene Therapy Products	https://www.fda.gov/media/175132/download
24	2016	Mitochondrial replacement therapy: the UK and US regulatory landscapes.	https://doi.org/10.1093/jlb/lsw051
25	2025	Exploring Regulatory Frameworks for Exosome Therapy: Insights and Perspectives.	https://pubmed.ncbi.nlm.nih.gov/32523983/
26	2023	Exosomes: A Promising Strategy for Repair, Regeneration and Treatment of Skin Disorders.	https://doi.org/10.3390/cells12121625
27	2021	Clinical applications for exosomes: Are we there yet?	https://doi.org/10.1111/bph.15432
28	2015	Regulation of unproven stem cell therapies – medicinal product or medical procedure?	https://www.eurostemcell.org/regulation-unproven-stem-cell-therapies-medicinal-product-or-medical-procedure
29	2024	Regulation of exosomes as biologic medicines: Regulatory challenges faced in exosome development and manufacturing processes.	https://pubmed.ncbi.nlm.nih.gov/39115257/
30		"Exogenous and Endogenous Dendritic Cell-Derived Exosomes: Lessons Learned for Immunotherapy and Disease Pathogenesis,"	https://doi.org/10.3390/cells11010115
31	2018	Advisory on Legal Restrictions on the Use of Mitochondrial Replacement Techniques to Introduce Donor Mitochondria into Reproductive Cells Intended for Transfer into a Human Recipient | FDA	https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/advisory-legal-restrictions-use-mitochondrial-replacement-techniques-introduce-donor-mitochondria
32	2025	Bulk Drug Substances Used in Compounding Under Section 503A of the FD&C Act | FDA	https://www.fda.gov/drugs/human-drug-compounding/bulk-drug-substances-used-compounding-under-section-503a-fdc-act
33	2019	Federal Register: Amendments to	https://www.federalregister.gov/documents/201

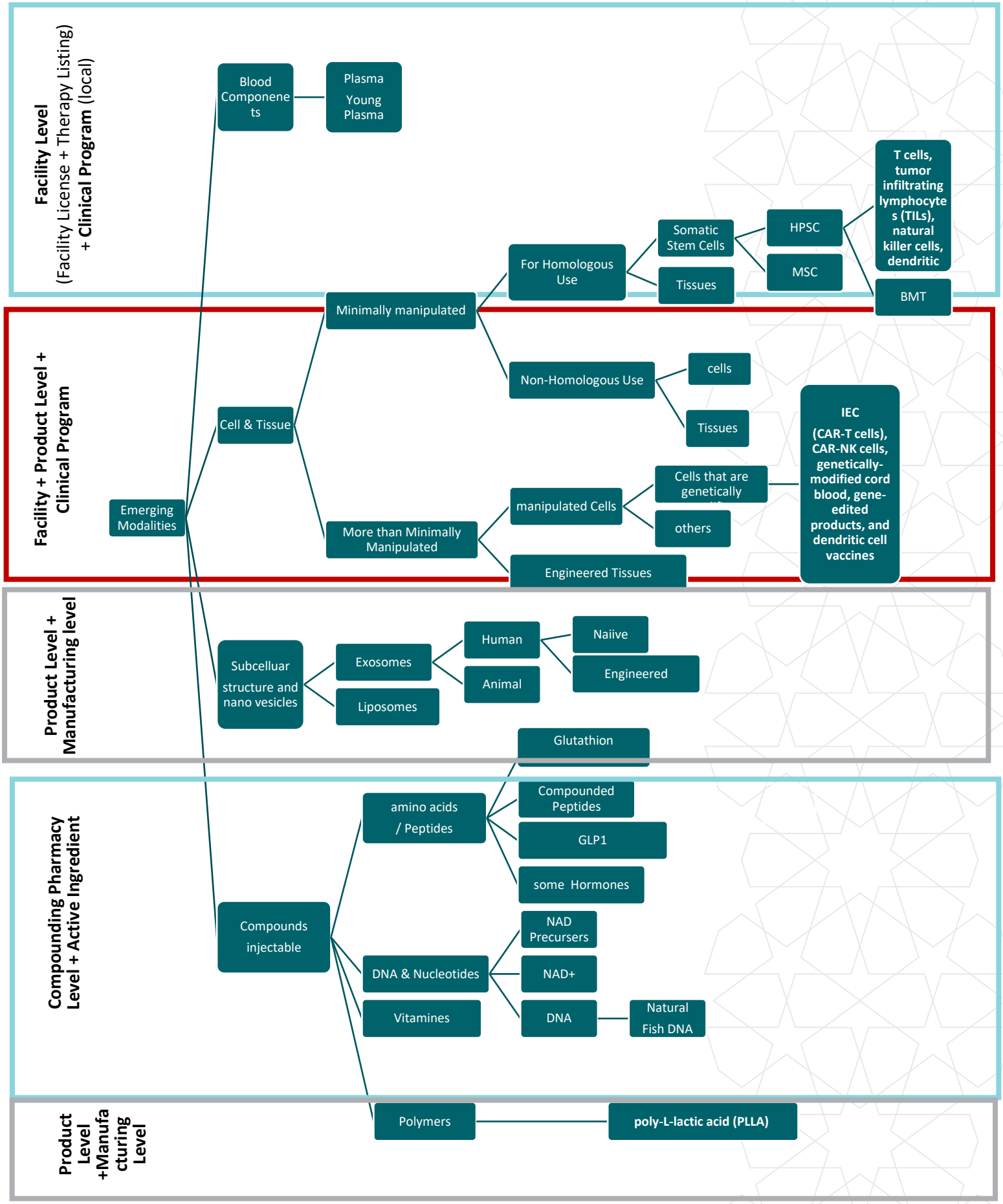
		the List of Bulk Drug Substances That Can Be Used to Compound Drug Products in Accordance With Section 503A of the Federal Food, Drug, and Cosmetic Act	9/09/05/2019-18951/amendments-to-the-list-of-bulk-drug-substances-that-can-be-used-to-compound-drug-products-in
34	2025	FDA's Concerns with Unapproved GLP-1 Drugs Used for Weight Loss | FDA	https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/fdas-concerns-unapproved-glp-1-drugs-used-weight-loss
35	2019	USP, Chapter 797 PHARMACEUTICAL COMPOUNDING—STERILE PREPARATIONS	https://www.uspnf.com/sites/default/files/usp_pdf/EN/USPNF/revisions/gc-797-postponement-rb-notice-20191122.pdf
36	2016	USP, Sterility Test	https://www.usp.org/sites/default/files/usp/document/harmonization/gen-method/q11_pf_ira_34_6_2008.pdf
37	2012 / 2018	Guidance for Industry: Pyrogen and Endotoxins Testing: Questions and Answers	https://www.fda.gov/regulatory-information/search-fda-guidance-documents/guidance-industry-pyrogen-and-endotoxins-testing-questions-and-answers
38	NA	USP <788> PARTICULATE MATTER IN INJECTIONS	https://www.uspnf.com/sites/default/files/usp_pdf/EN/USPNF/revisionGeneralChapter788.pdf
39	2024	USP Compounding Standards and Beyond-Use Dates (BUDs)	https://www.usp.org/sites/default/files/usp/document/our-work/compounding/usp-bud-factsheet.pdf
40	2023,	USP 797 Key Changes	https://www.ashp.org/-/media/assets/pharmacy-practice/resource-centers/compounding/docs/USP-797-Key-Changes.pdf
41	2019	Appropriate Dosing for Parenteral Nutrition: ASPEN Recommendations,	https://nutritotal.com.br/pro/wp-content/uploads/2019/04/PN-DosingASPEN.pdf
42	2024	Mayo Clinic, IV Vitamin therapy: Understanding the lack of proven benefit and potential risks of this health fad	https://mcpress.mayoclinic.org/living-well/iv-vitamin-therapy-understanding-the-lack-of-proven-benefit-and-potential-risks-of-this-health-fad/
43	2012	INFUVITE ADULT (PHARMACY BULK PACKAGE) Label	https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/021559s015lbl.pdf
44	2020	Definition of the Term "Biological Product" Final Regulatory Impact Analysis | FDA	https://www.fda.gov/media/135421/download?attachment

45	2018	Glutathione for skin lightening: a regnant myth or evidence-based verity?	https://pubmed.ncbi.nlm.nih.gov/29445569/
46	2022	FDA Seeks to Ban Compounded Glutathione, AANP Responds with Call-to-Action - American Association of Naturopathic Physicians	https://naturopathic.org/news/607314/FDA-Seeks-to-Ban-Compounded-Glutathione-AANP-Responds-with-Call-to-Action.htm
47	2024	FDA reminds compounders to use ingredients suitable for sterile compounding | FDA.	https://www.fda.gov/drugs/human-drug-compounding/fda-reminds-compounders-use-ingredients-suitable-sterile-compounding
48	2022	Polydeoxyribonucleotide: A promising skin anti-aging agent,	https://doi.org/10.1016/j.cjprs.2022.09.015
49	2023	IV Hydration Clinics | Safety Concerns | Panel Discussion	https://nabp.pharmacy/wp-content/uploads/2023/08/Hydration-Resources.pdf
50	2017	FDA's human drug compounding progress report: Three years after enactment of the drug quality and security act.	https://www.fda.gov/drugs/human-drug-compounding/fdas-human-drug-compounding-progress-report-three-years-after-enactment-drug-quality-and-security
51	2025	A prohibited peptide and an unapproved drug found in health and wellness products—OPSS is an initiative focused on dietary supplements, performance-enhancing substances, and related health & safety issues BPC-157	https://www.opss.org/article/bpc-157-prohibited-peptide-and-unapproved-drug-found-health-and-wellness-products
52	2024	Stable gastric pentadecapeptide BPC 157 and intestinal anastomoses therapy in rats—A review.	https://pubmed.ncbi.nlm.nih.gov/39204186/
53	2025	Injectable therapeutic peptides—an adjunct to regenerative medicine and sports performance?	https://pubmed.ncbi.nlm.nih.gov/39204186/
54	2006	Once-daily administration of CJC-1295, a long-acting growth hormone-releasing hormone (GHRH) analog, normalizes growth in the GHRH knockout mouse.	https://journals.physiology.org/doi/full/10.1152/ajpendo.00201.2006
55	2024	Preclinical Animal Study and Pilot Clinical Trial of Using Enriched Peripheral Blood-Derived Mononuclear Cells for Intervertebral Disc Degeneration.	https://pubmed.ncbi.nlm.nih.gov/38173231/

57	2022	"Large-Scale Production of Extracellular Vesicles: Report on the 'Massivevs' ISEV Workshop,"	https://doi.org/10.1002/jex2.63
58	2023	Efficacy and safety of platelet-rich plasma and autologous-serum eye drops for dry eye in primary Sjögren's syndrome: a randomized trial.	https://doi.org/10.1038/s41598-023-46671-
59	2021	FACT-JACIE International Standards for HEMATOPOIETIC CELLULAR THERAPY Product Collection, Processing, and Administration 8th edition (8.1)	https://www.ebmt.org/sites/default/files/2025-10/STS_5_2_041_FACT-JACIE%20Standards%20Eighth%20Edition_8_1_R2_12142021_ForWeb.pdf
60	2019	FACT: Frequently Asked Questions_ Standards for Immune Effector Cells (1223_1).pdf	https://www.factglobal.org/media/j4iemdvd/sts_faq_5_002_faqsstandardsforimmuneeffectorcells_r1_02132019-w.pdf
61	2022	FACT Common Standards | FACT , third edition	https://www.factglobal.org/standards/common-standards
62	2019	Public Safety Notification on Exosome Products | FDA	https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/public-safety-notification-exosome-products
63	2025	Certain Bulk Drug Substances for Use in Compounding that May Present Significant Safety Risks | FDA	https://www.fda.gov/drugs/human-drug-compounding/certain-bulk-drug-substances-use-compounding-may-present-significant-safety-risks
64	2019	FDA highlights concerns with using dietary ingredient glutathione to compound sterile injectables | FDA	https://www.fda.gov/drugs/human-drug-compounding/fda-highlights-concerns-using-dietary-ingredient-glutathione-compound-sterile-injectables#:~:text=FDA%20received%20a%20report%20concerning,ranging%20from%20fever%20to%20death.
65	NA	COMPLIANCE PROGRAM GUIDANCE MANUAL Inspection of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps) 7341.002	https://www.fda.gov/media/73949/download
66	2014 Updated 2019	Biologics License Applications for Minimally Manipulated, Unrelated Allogeneic Placental/Umbilical Cord Blood Intended for Hematopoietic and Immunologic Reconstitution in Patients with Disorders Affecting the Hematopoietic System	http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm
68	2020	Regulatory Considerations for Human Cells, Tissues, and Cellular and Tissue-Based Products: Minimal Manipulation and Homologous Use	https://www.fda.gov/regulatory-information/search-fda-guidance-documents/regulatory-considerations-human-cells-tissues-and-cellular-and-tissue-based-

			products-minimal
61	2025	"21 CFR Part 1271". National Archives, US Government	https://www.ecfr.gov/current/title-21/chapter-I/subchapter-L/part-1271
64	2010	"WHO guiding principles on human cell, tissue, and organ transplantation"	https://www.who.int/publications/i/item/WHO-HTP-EHT-CPR-2010.01
66	NA	Coverage with evidence development, Autologous Platelet-rich Plasma. Centers for Medicaid and Medicare Services	https://www.cms.gov/medicare/coverage/evidence/plasma
67	2020	Growth factor concentrations in platelet-rich plasma for androgenetic alopecia: an intra-subject, randomized, blinded, placebo-controlled, pilot study.	https://pubmed.ncbi.nlm.nih.gov/31984508/
68	2016	A mechanistic Model of platelet-rich plasma treatment for androgenetic alopecia.	https://pubmed.ncbi.nlm.nih.gov/27631460/
69	2024	Standard For Stem Cell Therapies Products and Regenerative Medicine (To Be Replaced by This Standard) Would Be Applicable for the Transition Period	https://www.doh.gov.ae/en/resources/standards
70	2024	Standard on Biobanking of Stem Cells	https://www.doh.gov.ae/en/resources/standards
71	2019	Doh Standard for Center of Excellence in Hematopoietic Stem Cell Transplantation Services for Adults and Pediatrics	https://www.doh.gov.ae/en/resources/standards
72	2024	Precision Medicine Policy	https://www.doh.gov.ae/en/resources/policies
73	2024	Policy on Biobanking	https://www.doh.gov.ae/en/resources/policies
74	2024	Standard for Pan-Human Biobanks	https://www.doh.gov.ae/en/resources/standards
75	2024	Guidelines for HCT Indications and Timing of Referral for Adult and Pediatric	https://www.doh.gov.ae/en/resources/guidelines

Appendix 1: Class Based Framework



Appendix 2: Banned peptides for compounding or sourcing in unregistered commercially available products

Peptide	Properties and unproven use	Concerns behind the banning
1 AOD-9604	AOD-9604 is illegitimately used by bodybuilders for its purported ability to speed up metabolism, burn stubborn fat, and amp muscle growth by boosting human growth hormone and curbing insulin resistance[49] AOD-9604 is popular among people looking to boost muscles.	AOD-9604 has "risk for immunogenicity (the ability to trigger a negative immune reaction), peptide-related impurities, and limited safety-related information."
2 BPC-157 **Other names:** **(Body Protection Compound-157)** **PL 14736 (pharmaceutical code used in early studies)** **BPC-15 (older, shorter version of the peptide) Pentadecapeptide** **BPC-157 (scientific name indicating 15 amino acids)** **Gastric pentadecapeptide BPC-157** **Bepecin *(used in some commercial/research references)***	*BPC-157 is not a dietary ingredient.* It is an unapproved drug and cannot be legally prescribed or sold over the counter. BPC-157 is listed in class S0: Non-Approved Substances on the World Anti-Doping Agency's (WADA) Prohibited List and, it's also on the *Operation Supplement Safety (OPSS) (an initiative focused on dietary supplements, performance-enhancing substances, and related health & safety issues)* Prohibited Dietary Supplement Ingredients List [51] Products containing BPC-157 might be labeled as "research chemicals" and carry statements such as "Not for human consumption," "Research use only," or "For research purposes only." *The use of "research chemicals" or any products containing prohibited ingredients which are required to be avoided,* regardless of how they are taken (by mouth, injection, or nasal spray).	There are many research studies on the potential use of BPC-157 in treatments for a variety of medical conditions. Although it was registered in a clinical trial under the name Bepecin in 2015, the study did not result in any approved uses for this substance. In addition, the marketed benefits of BPC-157 have only been shown in lab or animal studies (rats, mice, and dogs). The lack of well-designed, comprehensive, human clinical studies means that *there is little to no reliable scientific evidence to support the safety or effectiveness of BPC-157 in humans*[52,53] US-FDA has also cautioned against compounded drugs containing BPC-157 due to safety risks and potential contamination with other substances.
3 CJC-1295	CJC-1295 used illegally as a longevity-supporting peptide, touting better sleep, increased muscle mass and weight loss, boosted cognitive and immune	According to the FDA, CJC-1295 carries a risk for increased heart rate and cardiac events. Additionally, compounded CJC-1295 runs the risk of

Appendix 2: Banned peptides for compounding or sourcing in unregistered commercially available products

Peptide	Properties and unproven use	Concerns behind the banning
	function, and slowed skin aging[54] in animal studies.	peptide impurities and harmful immune responses.
4 Cathelicidin LL-37 **Cathelicidin antimicrobial peptide (LL-37)**	Cathelicidin LL-37 is a natural human antimicrobial and immunomodulatory peptide derived from the hCAP-18 precursor. It has broad antimicrobial, wound-healing, and immune-balancing effects, but no approved medical or cosmetic use globally. Products claiming to contain or deliver LL-37 are unapproved biologics, considered experimental and banned in sports.	Compounded drugs containing cathelicidin LL-37 may pose risk for immunogenicity for certain routes of administration and may have complexities with regard to peptide-related impurities and API characterization. FDA lacks sufficient safety-related information regarding cathelicidin LL-37 to know whether the drug would cause harm when administered to humans. Nonclinical research findings suggest detrimental effects on male reproduction and that this drug can be protumorigenic in some tissues. Prohibited by WADA under S0
5 Emideltide (DSIP) **Common name: Delta Sleep–Inducing Peptide (DSIP)**	Emideltide, also known as Delta Sleep-Inducing Peptide (DSIP), is Endogenous nonapeptide (short neuropeptide) a naturally occurring neuropeptide from the hypothalamus of rabbits during studies on sleep regulation. It has since been synthetically produced and marketed as Emideltide, primarily in eastern European countries, for its neuromodulatory and stress-adaptive effects. Parenteral (intramuscular, subcutaneous, intravenous) or intranasal It is unapproved in the U.S., EU, and UAE, and any compounded or peptide-clinic version elsewhere is experimental and unregulated.	Compounded drugs containing emideltide may pose risk for immunogenicity for certain routes of administration and may have complexities with regard to peptide-related impurities and API characterization. FDA has not identified safety-related information regarding emideltide for the proposed route of administration. Therefore, the agency lacks sufficient information to know whether the drug would cause harm if administered to humans. WADA Prohibited under S0
6 Epitalon **Ala–Glu–Asp–Gly (Alanine–Glutamic**	Epitalon (also spelled Epithalon or Epithalamin) is a synthetic tetrapeptide (Ala–Glu–Asp–Gly) developed from a natural pineal gland extract called Epithalamin.	Compounded drugs containing epitalon may pose risk for immunogenicity for certain routes of administration due to the potential for aggregation and peptide-related

Appendix 2: Banned peptides for compounding or sourcing in unregistered commercially available products

Peptide	Properties and unproven use	Concerns behind the banning
acid–Aspartic acid–Glycine)	Epitalon is claimed to activate telomerase, restore circadian function, and modulate aging processes. It is used in some eastern Europe countries as a geroprotective and immune-supportive peptide, but it is not approved by FDA, EMA, or UAE regulators. All commercial "anti-aging" or "longevity" peptide formulations containing Epitalon are considered experimental, unregulated, and prohibited in sports.	impurities. US-FDA has not identified safety-related information regarding epitalon for the proposed route of administration. Therefore, the agency lacks sufficient information to know whether the drug would cause harm if administered to humans.
7 GHK-Cu (for injectable routes of administration)	Copper tripeptide-1 (GHK-Cu) GHK-Cu acts as a bioregulatory signal peptide that delivers copper to cells and triggers tissue repair, antioxidant, and anti-inflammatory pathways. GHK-Cu is recognized only as a cosmetic ingredient 8(topical use) in USA and Europe. Any injectable form is unapproved	Compounded injectable drugs containing GHK-Cu may pose risk for immunogenicity due to the potential for aggregation and peptide-related impurities. There are limited data in humans to inform safety-related considerations.
8 Growth hormone releasing peptide-2 (GHRP-2) (for injectable and nasal routes of administration)	GHRP-2 is a synthetic ghrelin-mimetic peptide that transiently increases growth-hormone release. It is unapproved for any medical use, whether injectable or nasal, and its sale or clinical administration for "anti-aging," "muscle growth," or "wellness" purposes is illegal and unsafe. Only topical research or controlled laboratory studies are legitimate contexts. All synthetic GHRPs (-2, -6, ipamorelin, hexarelin) are prohibited in sports and human compounding under FDA, EMA, and UAE regulations.	Compounded drugs containing GHRP-2 for injectable and nasal administration may pose risk for immunogenicity due to the potential for aggregation and peptide-related impurities. GHRP-2 also contains an unnatural amino acid, which adds to the complexity of peptide characterization. FDA is aware of reports of serious adverse advents in patients who received GHRP-2, including increased insulin requirement to maintain the blood glucose level, death of critically ill study subjects, infection and pancreatitis, though causality has not been established.

Appendix 2: Banned peptides for compounding or sourcing in unregistered commercially available products

Peptide	Properties and unproven use	Concerns behind the banning
9 **Growth hormone releasing peptide-6 (GHRP-6)**	Growth Hormone Releasing Peptide-6 (GHRP-6) is a synthetic hexapeptide that acts as a potent growth-hormone secretagogue — meaning it stimulates the pituitary gland to release growth hormone (GH). It belongs to the same pharmacological family as GHRP-2, Ipamorelin, and Hexarelin, all of which mimic the natural hunger hormone ghrelin. It is not approved for medical use anywhere and is prohibited in sports. While it has legitimate research value in endocrinology, any injectable or nasal administration in humans outside regulated studies is unsafe and illegal.	Compounded drugs containing GHRP-6 may pose risk for immunogenicity for certain routes of administration due to the potential for aggregation and peptide-related impurities. FDA has identified limited safety-related information, but the available data reveal safety concerns including potential effect on cortisol and increase in blood glucose due to decreases in insulin sensitivity.
10 **Ibutamoren mesylate**	Is a none petide compound, however the table has it out of precautionary measure	Ibutamoren mesylate poses significant safety risks due to the potential for congestive heart failure in certain patients. The agency is aware of a randomized, placebo-controlled trial assessing ibutamoren mesylate for the treatment of patients recovering from hip fracture that “was terminated early due to a potential safety signal of congestive heart failure.”
11 **Ipamorelin acetate**	Ipamorelin acetate is a synthetic pentapeptide belonging to the growth hormone–releasing peptide (GHRP) family, developed as a selective ghrelin receptor agonist (GHS-R1a) that stimulates the release of growth hormone (GH) from the pituitary gland. it remains unapproved for any medical indication worldwide. Injectable or nasal products marketed for “anti-aging,” “muscle growth,” or “GH optimization” are unregulated, illegal, and potentially unsafe.	Compounded drugs containing Ipamorelin acetate may pose risk for immunogenicity for certain routes of administration due to the potential for aggregation or peptide-related impurities. Ipamorelin acetate also contains unnatural amino acids, which add to the complexity of peptide characterization. A study published in literature identified serious adverse events including death when ipamorelin was administered intravenously for improving gastric motility. FDA has not identified safety-related information regarding

Appendix 2: Banned peptides for compounding or sourcing in unregistered commercially available products

Peptide	Properties and unproven use	Concerns behind the banning
		ipamorelin acetate via certain other injectable routes of administration. Therefore, the agency lacks sufficient information to know whether the drug would cause harm if administered to humans via those routes.
12 Kisspeptin-10	Kisspeptin-10 is a synthetic decapeptide (10–amino-acid) fragment of the natural reproductive hormone kisspeptin, which plays a central role in regulating puberty onset, fertility, and reproductive hormone secretion through the hypothalamic–pituitary–gonadal (HPG) axis. It is an experimental neuropeptide — highly important in reproductive endocrinology — but not approved for clinical use anywhere in the world. Injectable or nasal products promoted for "fertility enhancement," "testosterone boosting," or "anti-aging" use are unapproved, illegal, and potentially harmful.	Compounded drugs containing Kisspeptin-10 may pose risk for immunogenicity for certain routes of administration and may have complexities with regard to peptide-related impurities and API characterization. FDA has no, or only limited, safety-related information for the proposed routes of administration. Therefore, the agency lacks sufficient information to know whether the drug would cause harm when administered to humans.
13 KPV	KPV is a short synthetic bioactive peptide — a tripeptide consisting of the amino acids Lysine–Proline–Valine. It is a naturally occurring fragment of the hormone alpha-melanocyte-stimulating hormone (α-MSH), which is part of the POMC (proopiomelanocortin) family.	FDA has not identified any human exposure data on drug products containing KPV administered via any route of administration. FDA lacks important information regarding any safety issues raised by KPV, including whether it would cause harm if administered to humans.
14 Mechano growth factor pegylated (PEG-MGF)	MGF (and its PEG-modified form) has become widely mentioned in sports, bodybuilding, and experimental regenerative medicine, but no PEG-MGF product is approved anywhere for medical use.	Compounded drugs containing Mechano Growth Factor Pegylated (PEG-MGF) may pose significant risk for immunogenicity for certain routes of administration and may have complexities with regard to peptide-related impurities and API

Appendix 2: Banned peptides for compounding or sourcing in unregistered commercially available products

Peptide	Properties and unproven use	Concerns behind the banning
	as a synthetic IGF-1–derived peptide engineered to extend the activity of natural MGF, which promotes muscle repair and regeneration after mechanical stress. It has never been approved for medical or human use anywhere. All injectable PEG-MGF products are unregulated research chemicals, and their administration poses unknown systemic and oncogenic risks. It is prohibited in sports, and unsafe in clinical or aesthetic use outside controlled laboratory studies.	characterization. FDA has not identified any human exposure data on drug products containing PEG-MGF administered via any route of administration. FDA lacks important information regarding any safety issues raised by PEG-MGF, including whether it would cause harm if administered to humans.
15 Melanotan II	Melanotan II (also known as MT-II) is a synthetic cyclic heptapeptide analog of the human melanocortin hormone α-MSH (alpha-melanocyte-stimulating hormone). It was originally developed as a research compound to stimulate skin pigmentation and explore sexual function modulation, but it has never been approved as a medicine anywhere in the world. Despite this, it is frequently sold online or through "tanning clinics" as an unregulated injectable or nasal peptide, posing significant health and legal risks. Melanotan II is a synthetic α-MSH analog that darkens skin and increases libido by activating melanocortin receptors. It is not an approved drug in any country, and its use via injection or nasal spray carries serious safety, contamination, and cancer-risk concerns. Only the related compound	Compounded drugs containing Melanotan II may pose risk for immunogenicity for certain routes of administration due to the potential for aggregation or peptide-related impurities. Published case reports discuss serious adverse events including melanoma, posterior reversible encephalopathy syndrome, sympathomimetic toxidrome and priapism

Appendix 2: Banned peptides for compounding or sourcing in unregistered commercially available products

Peptide	Properties and unproven use	Concerns behind the banning
	Bremelanotide (PT-141) is legally approved — and for sexual dysfunction only, not tanning.	
16 **MOTs-C Mitochondrial ORF of the 12S rRNA type-C (MOTS-C)**	short for Mitochondrial-derived Peptide, MOTS-C) is a bioactive peptide encoded by the mitochondrial genome, not the nuclear genome — a rare and fascinating feature that links it to energy regulation, metabolism, and cellular stress responses. MOTS-C acts as a metabolic regulator and cell-protective signal. It's often described as a "mitokine" — a signaling peptide released from mitochondria that influences nuclear gene expression. Only *early-phase* and *very limited*. Some small studies explore MOTS-C in metabolic syndrome, exercise performance, and aging, but no approved therapeutic indication exists. It is not an approved drug, supplement, or cosmetic ingredient in any major jurisdiction. Any marketed MOTS-C product is unregulated, illegal to sell for human use, and prohibited in sports	Compounded drugs containing MOTs-C may pose significant risk for immunogenicity for certain routes of administration and may have complexities with regard to the peptide-related impurities and API characterization. FDA has not identified any human exposure data on drug products containing MOTs-C administered via any route of administration. FDA lacks important information regarding any safety issues raised by MOTs-C, including whether it would cause harm if administered to humans. On WADA banned list: *Banned* under S0 — Non-approved substances
17 **Semax (heptapeptide):** **Met-Glu-His-Phe-Pro-Gly-Pro**	Semax is a synthetic heptapeptide (seven–amino acid) neuropeptide originally developed as a nootropic and neuroprotective drug. It is not approved by the FDA, EMA, or other major regulators but is used medically in eastern Europe countries. Derived from it is adrenocorticotropic hormone (ACTH) fragment 4–10, but lacks hormonal (steroidogenic) activity.	Compounded drugs containing semax (heptapeptide) may pose risk for immunogenicity for certain routes of administration due to the potential for aggregation and peptide-related impurities. FDA has no, or limited, safety-related information for proposed routes of administration. Therefore, the agency lacks sufficient information to know whether the drug would cause harm if administered to humans.

Appendix 2: Banned peptides for compounding or sourcing in unregistered commercially available products

Peptide	Properties and unproven use	Concerns behind the banning
	Route of administration Typically intranasal; also used as injectable in research settings.	
18 Thymosin beta-4, fragment (LKKTETQ)	Thymosin beta-4 (Tβ4) is a 43-amino-acid naturally occurring peptide found in almost all human and animal cells. It belongs to the β-thymosin family, which regulates actin dynamics — crucial for cell migration, tissue repair, angiogenesis, and wound healing. Thymosin β-4 fragment (LKKTETQ) is a synthetic 7-amino-acid sequence corresponding to the active actin-binding domain of the natural Thymosin β-4 peptide. It shows some biological activity in vitro, but has no approved medical use. Products containing this fragment are unregulated, not authorized for human use, and prohibited in sports.	Compounded drugs containing thymosin Beta-4, Fragment (LKKTETQ) may pose risk for immunogenicity for certain routes of administration due to the potential for aggregation as well as peptide-related impurities. FDA has not identified any human exposure data drug products containing Thymosin Beta-4, Fragment. FDA lacks important information regarding any safety issues raised by this drug, including whether it would cause harm if administered to humans.
19 Selank acetate (TP 7) **TP-7 (Thymogen Peptide-7)**	Selank acetate (TP-7) is a synthetic heptapeptide (seven–amino-acid) neuropeptide developed as an anxiolytic (anti-anxiety) and nootropic (cognitive-enhancing) compound. It is chemically related to tuftsin, a natural immunomodulatory tetrapeptide derived from the IgG molecule, and was designed to combine immunomodulatory and neuro-modulatory activity. Selank acetate (TP-7) is a synthetic heptapeptide neuropeptide that acts as an anxiolytic and nootropic through modulation of GABA, serotonin, and neurotrophic factors. It is approved in Eastern European countries for anxiety	Compounded drugs containing selank acetate may pose risk for immunogenicity for certain routes of administration due to the potential for aggregation and peptide-related impurities. FDA lacks important information regarding any safety issues raised by selank acetate administered to humans.

Appendix 2: Banned peptides for compounding or sourcing in unregistered commercially available products

Peptide	Properties and unproven use	Concerns behind the banning
	and cognitive disorders but remains unapproved in the U.S., EU, and UAE, where it is treated as an experimental or unregulated peptide. Products marketed in wellness or longevity clinics are not licensed medicines and fall under "unapproved peptide" classification.	
20 Thymosin-alpha 1 (Ta1) **INN: Thymalfasin** **Common names: Thymosin α1, Tα1, Ta1**	Thymosin α1 (Ta1 / Thymalfasin) is a 28-amino-acid immune-modulating peptide that enhances T-cell-mediated antiviral and antitumor defense. It is approved in several countries for chronic hepatitis and immune deficiency but not approved by FDA or EMA. All non-registered or compounded versions are considered unapproved biologics and banned in sports.	Compounded drugs containing thymosin-alpha-1 (Ta1) may pose significant risk for immunogenicity for certain routes of administration and may have complexities with regard to peptide-related impurities and API characterization. The safety-related information is inadequate for the agency to sufficiently understand the extent of any safety issues raised by the proposed compounded drug. Prohibited by WADA: Classified as "non-approved peptide or experimental substance."

Appendix 3: Classification application: minimum information to be provided for the classification of Human Cell-Based / Tissue Based Therapies

Criterion	Description
Information about the applicant	Background information about the applicant, its capabilities, know how source, accreditation and licensed with the proof documents attached
Degree of Manipulation	Outline the processing steps starting from the source sample up to administration. Provide the justification for considering minimally manipulated vs more than minimally manipulated
Intended Use	Provide the intended use, the indications where the therapy will be prescribed and administered, Provide justification why consider homologous versus non-homologous use.
Mechanism of Action	Provide a brief explaining the expected Systemic effects or dependence on metabolic activity Examines pharmacological, immunological, or metabolic (PIM) action and / or tissue regeneration/repair.
Source of Cells	Provide a brief on the starting human sample and explain if autologous, allogeneic,
Route of administration	Route of administration
Combination / use of regulated Medical Devices	Provide a brief on the administration and if there will be a combination with medical device, Also include a brief on the kits to be sued for collection and separation

Appendix 4: Table of content for applications for Cell -Based therapies minimally manipulated for homologous use and non- homologous Use

1. **Administrative Information:**

- Ref Number from DoH
- Sponsor's Submission Date
- Status (Clinical studies phase)
- Date
- applicant Information
- Applicant Point of Contact
- Title of the cell therapy
- Proposed Use
- Product Description
- Introduction/Rationale: must include the classification of the product and the category for the non-Homologous use along with the rationale>
- Associated therapy protocol for Homologous use or approved non homologous use
- clinical trial protocol as (for non- homologous use) is therapy is not approved by reference regulatory body.

Product Manufacturing and Characterization:

- Flow Chart detailing steps and in process quality controls, along with another flow chart detailing the facilities in each step
- Product Manufacturing - Components
    - Cells
        - Allogeneic or Autologous Cell Components
            - Cell Source
            - Method of Collection
            - Donor Screening
            - Description
            - Tabulation of Testing
    - Cell Bank System (if applicable)
        - Master Cell Bank (MCB)
            - Description
            - Tabulation of Testing
            - Working Cell Bank (WCB)
                - Description
                - Tabulation of Testing

- Reagents
    - Tabulation of Reagents Used in Manufacture
    - Qualification Program
    - Determination of Removal of Reagents from Final Product
- Combination Products (if applicable)
- Drug or Device Components (if applicable)
- Any Early Scientific advice and Issues raised
- Areas of Concern for Components

2. Product Manufacturing - Procedures:

- Preparation of Autologous or Allogeneic Cells
    - Method of Cell Collection/Processing/Culture Conditions
    - Irradiation (if applicable)
- Process Timing & Intermediate Storage
- Final Harvest
    - Timing/Methods/Wash Procedure
- Final Formulation
    - Formulation/Infusion Buffer
    - Excipients
    - Cell Density/Concentration in the Final Product
    - Storage Method Prior to Use
- Areas of Concern for Manufacturing

3. Product Testing:

- In-Process Testing and Criteria
    - Tabulation of Tests, Manufacturing Step, Test Methods, Criteria, and Test Sensitivity & Specificity
    - Description of Test Methods
- Final Product Release Criteria/Specifications:
    - Tabulation of Final Product Release Criteria Tests, Test Methods, Criteria, Test Sensitivity & Specificity
    - Description of Test Methods

4. Product Stability:

- In-Process Stability Testing

    - Cryopreserved Cells
    - Other Intermediate Holding Steps
- Final Product Stability Testing
    - Product Formulation to Patient Infusion
    - Shipping Conditions

5. Other Issues:

- Product Tracking
- Labelling and Containers
    - In-Process Labelling
    - Final Product Labelling
    - Container Closure & Integrity
- Environmental Impact
- Validation and Qualification of the Manufacturing Process
    - QA/QC Program
    - Manufacturing Process Validation
- Biostatistics

6. Preclinical Studies

7. Clinical Studies:

- Protocol Title
- Subject Population
- Route of Administration
- Dose
- Frequency
- Genetic, Biochemical, and Immunological Testing
- Informed Consent

Appendix 5: Minimum Information to be Provided for the Classification of Exosome Products:

Details	Description
Information about the applicant	
Name	
Licensing information	
Accreditation information	
Documents attached	
Professional in Charge name and contact	
Product / therapy information	
Dosage form	
Formulation (active ingredients description) and strength (content)	
Source of the Exosomes (type of tissues or cells, source if human, animal or plant with exact description)	
Degree of Manipulation (Outline the processing steps starting from the source sample up to administration.)	
Processing / Manufacturing site	
Product qualification / certification (Provide description and attach all documents in relation to the product approval / qualification)	
Intended Use (Provide the intended use, the indications where the therapy will be prescribed and administered)	
Route of administration	
Mechanism of Action	Provide a brief explaining the expected Systemic effects
Combination / use of regulated Medical Devices	Provide a brief on the administration and if there will be a combination with medical device,
Others	

Appendix 6: Examples for classification of Human Cell-Based / Tissue-Based Therapies.

Table 1: Classification of cells examples/ Cell based products according to manipulation level

Description	Processing	Manipulation Classification / reason
Hematopoietic stem/progenitor cells	Administration of mobilizing agent to the donor to increase the number of circulating cells in the peripheral blood. Cell selection is performed on the mobilized peripheral blood apheresis product: to obtain a higher concentration of hematopoietic stem/progenitor cells for transplantation.	Is classified as minimally manipulated because the concentrated peripheral blood stem/progenitor cells are not altered with regard to their relevant biological characteristics to repopulate the bone marrow.
Terminally differentiated cells	Culturing hematopoietic stem/progenitor cells derived from Placental/umbilical cord blood under specific conditions.	More than minimally manipulated because the processing alters the cells' relevant biological characteristics of multipotency and capacity for self-renewal.
Ex vivo expanded hematopoietic stem/progenitor cell (HSPC) product derived from umbilical cord blood **Cord blood–derived hematopoietic stem/progenitor cell therapy** **Ex vivo expanded cord blood hematopoietic stem cell (HSC) product**	The following processes are conducted: • Cell selection (likely $CD34^+$ hematopoietic stem/progenitor cell enrichment). • Ex vivo culture in media in addition to growth factors. • Expansion: large numbers of cells capable of long-term bone marrow repopulation.	more than minimally manipulated because expansion changes key biological characteristics (gene expression, surface markers, multipotency, self-renewal). The processing affects the production of intracellular or cell-surface proteins and other markers of cell lineage, activation state, and proliferation, thereby altering the cells' relevant biological characteristics of multipotency and capacity for self-renewal.

Table 2: Cell /Cell based products classified according to homologous / non- homologous use

Description	Intended Use	Homologous / non-homologous
HPCs from mobilized peripheral blood	intended for transplantation into an individual with a disorder affecting the hematopoietic system that is inherited, acquired, or the result of myeloablative treatment.	Homologous use because the peripheral blood product performs the same basic function of reconstituting the hematopoietic system in the recipient.
HPCs from bone marrow	intended for infusion into an artery with a balloon catheter for the purpose of limiting ventricular remodeling following acute myocardial infarction.	Non- homologous use because limiting ventricular remodeling is not a basic function of bone marrow.
HPCs from cord blood	intended for intravenous infusion to treat cerebral palsy purportedly through the repair of damaged tissue in the brain through paracrine signaling or differentiation into neuronal cells.	Non- homologous use because there is insufficient evidence to support that repair of neurologic tissue through paracrine signaling or

		differentiation into neuronal cells is a basic function of these cells in the donor.
Cornea Graft transplanted	To treat patients with corneal blindness.	Homologous use because a corneal graft performs the same basic functions in the donor as in the recipient: which include protecting the eye and serving as its outermost lens
A cryopreserved vein or artery	used for arteriovenous access during hemodialysis	Homologous use because the vein or artery is supplementing the vessel as a conduit for blood flow. The basic functions of a include serving as a conduit for blood flow throughout the body.

Table 3: Tissue / Tissue Based Products classified according to Use

Tissue Description	Intended Use	Classification
Heart Valve Transplant	A heart valve is transplanted to replace a dysfunctional heart valve.	Homologous use because the donor heart valve performs the same basic function in the donor as in the recipient of ensuring unidirectional blood flow within the heart.
Pericardium is intended to be used as a wound covering for dura mater defects	The pericardium is intended to serve as a covering in the recipient, which is one of the basic functions it performs in the donor.	Homologous use
Amniotic membrane used for bone tissue replacement	used for bone tissue replacement to support bone regeneration following surgery to repair or replace bone defects	Non- homologous use because bone regeneration is not a basic function of amniotic membrane.
An amniotic membrane product	is used for wound healing and/or to reduce scarring and inflammation.	Non- homologous use because wound healing and reduction of scarring and inflammation are not basic functions of amniotic membrane.
amniotic membrane product is applied to the surface of the eye	to cover or offer protection from the surrounding environment in ocular repair and reconstruction procedures	Homologous use because serving as a covering and offering protection from the surrounding environment are basic functions of amniotic membrane.
Autologous pericardium	used to replace a dysfunctional heart valve in the same patient.	Non- homologous use because facilitating unidirectional blood flow is not a basic function of pericardium.
adipose tissue	Used for the repair, reconstruction, replacement, or supplementation of adipose tissue	Homologous use: In these situations, the Human Cell-Based / Tissue Based Therapy from adipose tissue is considered to be performing the same basic function in the recipient as in the donor.
A Human Cell Based / Tissue -Based Therapy from adipose tissue	for the treatment of a degenerative, inflammatory, or demyelinating disorder.	would generally be considered a non-homologous use
Adipose tissue	used to fill voids in the face or hands (e.g., for cosmetic reasons).	Homologous because providing cushioning and support is a basic function of adipose tissue.
A Human Cell Based / Tissue -Based Therapy from adipose tissue.	Used to treat musculoskeletal conditions such as arthritis or tendonitis by regenerating or	This is generally not considered a homologous use because regenerating or promoting the

Tissue Description	Intended Use	Classification
	promoting the regeneration of articular cartilage or tendon.	regeneration of cartilage or tendon is not a basic function of adipose tissue
A Human Cell Based / Tissue -Based Therapy from adipose tissue	is used to treat neurological disorders such as multiple sclerosis by limiting the autoimmune reaction and promoting remyelinization.	This is generally not considered a homologous use because limiting the autoimmune reaction and promoting remyelinization are not basic functions of adipose tissue
Adipose tissue	for transplantation into the subcutaneous areas of breast for reconstruction or augmentation procedures.	Homologous use because providing cushioning and support is a basic function of adipose tissue.
An acellular dermal product	is used for supplemental support, protection, reinforcement, or covering for a tendon.	Homologous use because in both anatomic locations, the dermis provides support and protects the soft tissue structure from mechanical stress.
An acellular dermal product	is used for tendon replacement or repair.	Non- homologous use because serving as a connection between muscle and bone is not a basic function of dermis.
Allogeneic mineralized or demineralized cortical human bone	is used to supplement the recipient's bone for repair, replacement, and reconstruction of bony voids or gaps involving the extremities, cranium, and spinal column; or for augmentation for posterior lateral fusions in the spinal column.	Homologous uses because in all locations, the HCT/P is supplementing the recipient's bone, for the purpose of supporting the body or protecting internal structures.
Pancreatic islets are transplanted into the liver through the portal vein: Islet cells may be separated from the pancreas of a deceased donor. The islet cells are then transplanted by injecting them into a vein that goes to the liver. The islet cells lodge in the small blood vessels of the liver, where they can live and produce insulin.	for preservation of endocrine function after pancreatectomy.	Allogenic- Homologous use because the regulation of glucose homeostasis is a basic function of pancreatic islets.

Table 4: Examples of Non-Homologous

Description	Intended / claimed / promoted use	Classification, status and pathway
Adipose-derived stem cells (SVF) marketed for systemic diseases **Stromal vascular fraction (SVF) cells isolated from adipose tissue**	Claimed uses: Alzheimer's disease, Parkinson's disease, COPD, diabetes, heart failure, autism.	More than minimally manipulated, Non-homologous: Adipose tissue's natural function is *cushioning and support*, not regenerating neurons, lung tissue, or insulin production. **Unproven Use, outside of this standard scope (as it is more than minimally manipulated.**
Amniotic fluid "stem cell" injections for joint disease and systemic conditions	Osteoarthritis, chronic pain, spinal cord injury, stroke recovery.	Non-homologous Amniotic fluid's function is to cushion the fetus in utero, not regenerate cartilage or nerves. If minimally manipulated: will follow this standard, however the u**se is unproven, will only be allowed after thorough evaluation provided clinical trial framework.**

Description	Intended / claimed / promoted use	Classification, status and pathway
Umbilical cord blood cells marketed for anti-aging or general wellness **Cord blood–derived mononuclear cells or MSCs**	Immune rejuvenation," anti-aging, longevity therapies	Not homologous Cord blood cells' natural function is hematopoietic reconstitution, not systemic anti-aging or wellness effects. If minimally manipulated: will follow this standard, however the u**se is unproven, will only be allowed after thorough evaluation provided clinical trial framework.**
skin removed from a donor and then transplanted in the same donor or matching donor	To cover a burn wound	Minimally manipulated Homologous use: **allowed after listing under the license of the clinical program owner and the administering clinics.**
replacement of a damaged or diseased cornea with a healthy cornea	Replacement generally means substitution of a missing tissue or cell	Minimally manipulated Homologous use: **allowed after listing under the license of the clinical program owner and the administering clinics.**
Donor-derived hematopoietic stem/progenitor cells (HSPCs) (e.g., bone marrow, peripheral blood stem cells, cord blood).	Placement into a recipient with a hematopoietic system disorder • inherited (e.g., sickle cell disease, thalassemia), • acquired (e.g., aplastic anemia, leukemia), • or secondary to myeloablative treatment (e.g., post-chemotherapy or radiation).	Homologous use: reason • The basic function of HSPCs in the donor is to form and reconstitute the hematopoietic system. • The intended clinical use in the recipient is to form and reconstitute the hematopoietic system. Therefore, it meets the homologous use criterion. Further to above, depending on processing/manipulation: • Case 1: Minimally manipulated (e.g., simple processing/cryopreservation) if used autologously or in a close relative. Conclusion: Minimally manipulated Homologous use: **Allowed after approving the application as indicated in this standard, and after listing under the DoH license of the clinical program owner and the administering clinics.** • Case 2: More than minimally manipulated (e.g., ex vivo expansion, gene modification, unrelated donor use) out of scope of this standard. Will require full regulatory assessment.
Implantation of dermal matrix into the facial wrinkles	to supplement a recipient's tissues	Minimally Manipulated Homologous uses **Allowed after approving the application as indicated in this standard, and after listing under the DoH license of the clinical program owner and the administering clinics.**
The use of bone chips	to supplement bony defects to be.	Minimally Manipulated Homologous uses **Allowed after approving the application as indicated in this standard, and after listing under the DoH license of the clinical program owner and the administering clinics.**

Table 5: Examples of classification combining the processing level and intended use all are minimally manipulated Homologous use. **Allowed after approving the application as indicated in this standard, and after listing under the DoH license of the clinical program owner and the administering clinics.**

Sample Type / Source	Processing / Manipulation	Intended Use	Classification
Adipose tissue (lipoaspirate, autologous)	Filtration / centrifugation only	Re-injection for padding/structural support	**Human Cell-Based / Tissue Based Therapy** — minimally manipulated, homologous use
Bone marrow aspirate (autologous)	Density gradient centrifugation	Hematopoietic reconstitution	**Human Cell-Based / Tissue Based Therapy** minimally manipulated homologous use
Corneal tissue (donor with matching…)	Stored in preservation medium	Transplant for vision restoration	**Tissue Based Therapy** — structural tissue, homologous use
Skin (autologous keratinocytes)	Minimal sheet preparation	Burn wound repair	**Human Cell-Based / Tissue Based Therapy** minimal manipulation, homologous
Placenta / amniotic membrane	Minimal prep (dehydration, sterilization)	Wound covering, anti-scarring	**Human Cell-Based / Tissue Based Therapy** minimally manipulated, homologous use
Oocytes / sperm (reproductive)	Cryopreservation, minimal handling	Fertility preservation / assisted reproduction	**Human Cell-Based / Tissue Based Therapy** reproductive exception

Table 6: Adipose Tissue vs Isolated Stem Cells

Type	Intended Use	Processing	Classification according to the level of manipulation	Explanation
Adipose tissue (as tissue, e.g., fat grafting):	Autologous fat transfer for cosmetic or reconstructive use	adipose tissue is harvested and only filtered/washed/centrifuged to remove contaminants	minimally manipulated **homologous use**	Adipose's primary function is structural cushioning/filling, and those properties remain intact.
Isolated stem cells from adipose tissue (stromal vascular fraction, SVF)		To get stem cells, the breakdown of the adipose matrix is needed (usually enzymatic digestion with collagenase) and then isolating the cellular fraction is done	more than minimal manipulation "Processing of adipose tissue to isolate nonstructural cells (e.g., SVF) is more than minimal manipulation	The structural properties of adipose are lost; the product is now a cellular therapy, not a structural tissue. Out of scope of this standard.