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Standard Guide for Processing Cells, Tissues, and Organs for Use in Tissue Engineered Medical Products[1]

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1. Scope

1.1 This guide describes the processing, characterization, production, and quality assurance of cells, tissues, and organs used for Tissue Engineered Medical Products (TEMPs). It concerns aspects of processing activities for cells, tissues, and organs to be further processed. These aspects include: (*1*) cell, tissue, and organ processing (that is, facility, reagents, and procedures for receipt, inspection, and storage; tissue culture components, biological risk factors, and processing area), (*2*) donors (human and nonhuman) and screening, and (*3*) cell, tissue, and organ characterization and processing.

1.2 This guide does not apply to any medical products of human origin regulated by the U.S. Food and Drug Administration (FDA) under 21 CFR Parts 16 and 1270 (**1**)[2] and 21 CFR Parts 207, 807, and 1271 (**2**).

1.3 *This standard does not purport to address all of the safety concerns, if any, associated with its use. It is the responsibility of the user of this standard to establish appropriate safety and health practices and determine the applicability of regulatory requirements prior to use.*

2. Terminology

2.1 *Definitions of Terms Specific to This Standard:*

2.1.1 *allogeneic or allogenic*, *adj*—cells, tissues, and organs in which the donor and recipient are genetically different individuals of the same species. Synonyms: *allograft* and *homograft*.

2.1.2 *autologous*, *adj*—cells, tissues, and organs in which the donor and recipient is the same individual. Synonyms: *autogenous*, *autograft*, or *autotransfusion*, a *self-to-self graft*.

2.1.3 *biological product*, *n*—"any virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product, or arsphenamine or its derivatives (or any trivalent organic arsenic compound) applicable to the prevention, treatment, or cure of diseases or injuries of man." (**3**) The term "analogous product" is interpreted to encompass somatic cell and gene therapy (21 CFR 600.3 (h)). A biological product may be used as a component of a TEMP. For the purposes of TEMPs, these biological products may be of any origin (that is, organism), tissue type, developmental stage, and may be living, non-living, and genetically or otherwise modified.

2.1.4 *cell culture*, *n*—the *in vitro* growth or maintenance of cells.

2.1.5 *cell*, *n*—"the smallest structural unit of an organism that is capable of independent functioning, consisting of one or more nuclei, cytoplasm, and various organelles, all surrounded by a semipermeable cell membrane." (**4**) Cells are highly variable and specialized in both structure and function, though all must at some stage synthesize proteins and nucleic acids, use energy, and reproduce. A cell or cells may be of any origin (that is, organism), tissue type, developmental stage, and may be living, non-living, and genetically or otherwise modified. Cells may be used as a component of a TEMP.

2.1.6 *combination product*, *n*—"As defined in 21 CFR § 3.2(e), the term "combination product" includes: (*1*) A product comprised of two or more regulated components, that is, drug/device, biologic/device, drug/biologic, or drug/device/biologic, that are physically, chemically, or otherwise combined or mixed and produced as a single entity; (*2*) Two or more separate products packaged together in a single package or as a unit and comprised of drug and device products, device and biological products, or biological and drug products; (*3*) A drug, device, or biological product packaged separately that according to its investigational plan or proposed labeling is intended for use only with an approved individually specified drug, device, or biological product where both are required to achieve the intended use, indication, or effect and where upon approval of the proposed product, the labeling of the approved product would need to be changed, for example, to reflect a change in intended use, dosage form, strength, route of administration, or significant change in dose; or (*4*) Any investigational drug, device, or biological product packaged separately that according to its proposed labeling is for use only with another individually specified investigational drug, device, or biological product where both are required to achieve the intended use, indication, or effect." Furthermore, "many somatic cell products administered to patients will be

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[2] The boldface numbers in parentheses refer to the list of references at the end of this standard.

combinations of a biological product and a device or of a drug, a biological product, and a device." (**5**) The term "combination product" may apply to TEMPs.

2.1.7 *cross-contamination*, *n*—the unintended presence of a cell or a material with another cell or material.

2.1.8 *disinfection*, *n*—the destruction or reduction of pathogenic and other kinds of microorganisms by thermal or chemical means (for example, alcohol, antibiotics, germicides).

2.1.9 *donor*, *n*—a living or deceased organism who is the source of cells or tissues, or both, for research or further processing for transplantation in accordance with established medical criteria and procedures.

2.1.10 *genetically modified*, *vt*—referring to cells, tissues, and organs of any origin that have an altered or modified genetic content.

2.1.11 *implantation*, *n*—the procedure of inserting materials such as a cell(s), tissue(s), or organ(s) for therapeutic purposes. Synonym: *graft* or *grafting*. TEMPs may be applied to a recipient by implantation or grafting.

2.1.12 *in-process control*, *n*—monitoring and, if necessary, adjustments performed to ensure that the process conforms to its specification. The control of the environment or equipment may be part of in-process control.

2.1.13 *organ*, *n*—a differentiated part of an organism that performs specific functions. Organs are biologic body parts, that after embryonic and early fetal stages, are composed of the four primary tissue types (that is, epithelial/mesothelial/endothelial, connective, muscular, and nervous tissues) that form a specific structure. For example, the intestine aids digestion and, simply put, it is composed of an epithelial lining, loose connective tissue, nervous tissue, and smooth muscle. An organ and its derivatives may be used as a component of a TEMP.

2.1.14 *processing*, *vt*—any activity performed on cells, tissues, and organs other than recovery, such as preparation and preservation for storage and packaging.

2.1.15 *processing materials*, *n*—any item or material that is not a component of the TEMP and is in contact with the cells, tissues, and organs during processing.

2.1.16 *recipient*, *n*—the individual or organism into whom materials are grafted or implanted.

2.1.17 *recovery*, *n*—the obtaining of cells or tissues which may be used for the production of TEMPs.

2.1.18 *reprocessing*, *vt*—the reworking of cells, tissues, and organs of unacceptable quality from a defined stage of processing, so that the quality may be rendered acceptable by one or more additional operations.

2.1.19 *stem cells*, *n*—progenitor cells capable of self-replication, proliferation, and differentiation.

2.1.20 *syngeneic*, *n*—cells, tissues, and organs in which the donor has an unreactive genotype with the recipient. Synonyms: *syngraft*, *isograft*, *isogeneic*, or *isogenic*.

2.1.21 *tissue*, *n*—a grouping of cells and extracellular matrix (that is, soluble and insoluble, fibrous and nonfibrous biological materials) that collectively have a specific structure and function. After embryonic and early fetal stages, there are four primary tissues which may have various forms: (*1*) epithelium, mesothelium, or endothelium, or combination thereof; (*2*) connective tissues (for example, adipose, blood, bone, and cartilage and loose connective tissue); (*3*) muscle tissue (that is, smooth, skeletal, cardiac); and (*4*) nerve tissue. Within a differentiated organ, all four primary tissue types are represented. A tissue and its derivatives may be used as a component of a TEMP.

2.1.22 *transplantation*, *n*—for therapeutic purposes, the process of implanting in one part, cells, tissue(s), or organ(s) taken from another part or from another individual. Transplantation in this sense is regulated by the U.S. Food and Drug Administration (FDA) under 21 CFR Parts 16 and 1270 (**1**) and 21 CFR Parts 207, 807, and 1271 (**2**).

2.1.23 *xenogeneic or xenogenic*, *n*—cells, tissues, and organs in which the donor and recipient belong to different species. Synonyms: *xenogenous*, *heterogeneic*, or *heterologous*.

2.1.24 *xenotransplantation*, *n*—any procedure that involves the transplantation or infusion into a human recipient of either (*1*) live cells, tissues, or organs from a nonhuman animal source or (*2*) human body fluids, cells, tissues, or organs that have had *ex vivo* contact with live nonhuman cells, tissues, or organs (24).

3. Significance and Use

3.1 This guide describes the general product development criteria and analyses applicable to processing of cells, tissues, and organs used for the production of TEMPs. For the purposes of this guide, cells, tissues, and organs may be derived from any organism at any developmental stage and in any state of health. For example, this guide applies to stem, progenitor, somatic, and germline cells, as well as cells from specific tissue and organ types. This guide also applies to cells, tissues, and organs from healthy, diseased, or injured embryos to adults.

3.2 Cells, tissues, and organs may be combined with a scaffold and may contain locally or systemically acting biomolecules or a drug (medicinal) product. This type of TEMP would be a "combination product."

4. Facility, Reagents, and Procedures

4.1 *Facility*:

4.1.1 *Receipt, Inspection, and Storage*—Facility issues including establishment of clean room classifications, training of personnel, environmental monitoring, sampling plans, and limits should comply with current good manufacturing practices (cGMP) (**6, 7**) and AATB standard for tissue banking related to good tissue practices (cGTP) (**8**). The FDA has proposed a new regulation on current good tissue practice (GTP) which, if finalized, would also be applicable, for example, FDA 21 CFR 1271 (**9**). All regions should be qualified using a rationale and scientifically sound qualification program that includes: (*1*) information on traceability, (*2*) assessment of risks for each material, and (*3*) the specific characterization tests. Guidelines for the storage of materials for processing can be found in FDA 21CFR 820 (**6**) as well as in GMP guidelines for shelf-life (**2, 8**).

4.2 *Reagents*:

4.2.1 *Tissue Culture Components*—All media and reagents used for the growth or maintenance of cells, tissues, and organs

should be manufactured under cGMP guidelines or be purchased from an organization that meets the guidelines (**6**). Ideally, all media and reagents should be of non-animal origin or contain no components of animal origin (**10**) to minimize the opportunity for virus or prion contamination and transmission. At the minimum, one should utilize media and reagents from organizations that have applied stringent sourcing controls and have validated terminal processes to minimize the risk of infection (**11**) It would be even more ideal, when working with animal cells, tissues, or derivatives, to obtain these biological materials from special breeding facilities (for instance, closed pathogen-free herds) and to include control ancestors.

4.2.1.1 *Basal Culture Media and Supplements*—Guidelines for sterile drug products produced by aseptic processing are published by CBER, 6/87 (**12**). Additional information concerning the use of basal media, supplements, recombinant, animal origin, non-animal origin, enzymes, feeder cells, substrates (two or three dimensional; exogenous versus endogenous), animal derived, non-animal derived, and other components of animal origin can be can be found in Brown et al. (**10**). Validation of aseptic filling for solution drug products is published by the PDA, 1980 (**13**). Quality assurance measures for acceptance of all components, including media, serum, and other additives should include records detailing source and lot numbers.

4.3 *Procedures*:

4.3.1 *Biological Risk Factors*:

4.3.1.1 *Adventitious Agents*—USFDA and WHO provide points to be considered regarding adventitious agents (**11**, **14**, **15**). Contamination by adventitious agents, including viruses such as HBV, HCV, or HIV, must be assessed (**6**, **16**, **17**). Media components and processing agents should be tested for the presence of pyrogens such as endotoxin. Typically, the Limulus Amebocyte Lysate (LAL) assay or chromogenic assay is used for this measurement (**16-18**). The LAL and the chromogenic assays are recommended by the FDA as an end-product test for endotoxin in human biologics and are listed in the USP (**16**). The validation of assays for pyrogenicity should follow prescribed protocols recommended by the FDA and the USP (**16-18**).

4.3.1.2 *Bioburden Testing*—Non-cellular components used for production of TEMPs must be sterilized and qualified as sterile, especially prior to the addition of living cells or other biological components (**19**). CFR 210 (**6**) and EN 12442 (**7**) indicated that if living cells are to be maintained in the final product, it is necessary to demonstrate that the cells, tissues, and organs are safe before their incorporation into the product whether derived from autologous, allogeneic, xenogeneic, or genetically modified sources. Other comments on this subject can be found in referenced documents (**11**, **15**, **20-24**).

4.3.2 *Processing Area*—Guidelines for the processing area must be followed to demonstrate qualified procedures and equipment which are able to keep contamination below a specified level (**19**, **25-27**).

4.3.2.1 *Environmental Monitoring Controls*—Environmental controls typically include establishing and maintaining clean room classifications at appropriate baseline levels through scheduled monitoring (**28**). cGMP guidelines should attempt to meet Class 100 requirements for critical aseptic processing operations (**6**, **19**). The adequacy of the clean room environment is monitored by close microbiological surveillance of air, water, surfaces, clean room, and personnel. Routine environmental monitoring with established alert levels can provide early warning on the adequacy of cleaning and sanitization procedures before action levels are exceeded. In addition to the environmental monitoring of the production area, products can be monitored for microbiological control during critical manufacturing steps (**19**, **26**, **29**, **30**).

4.3.2.2 *Preventive Maintenance Procedures and Routine Calibration*—Preventive maintenance procedures and calibration should be performed on equipment at scheduled intervals. Calibrations, where appropriate, should be against traceable standards, for instance U.S. National Institute of Standards and Technology (NIST) standards.

4.4 *Donor Screening*:

4.4.1 *Human Sources*—General donor suitability which covers aspects of testing for diseases (microbial and viral) and general safety can be completed by the manufacturer with validated tests methods or by CLIA certified testing laboratory (**6**). If using autologous donors, screening and testing of donor materials intended for transplantation is recommended and mandatory for allogeneic sources (**1**). Donor specimens must be tested and found to be negative, using FDA licensed donor screening tests in accordance with manufacturer's instructions, for HIV types I and II, hepatitis B and C, *Treponema pallidum*, human t-lymphotropic virus types 1 and 2, and cytomegalovirus in leukocyte rich cells and tissues (**6**, **21**, **31**).

4.4.2 *Donor Records and Archiving of Samples*—The donor's species, age, sex, and cell, tissue, and organ origin data (including country of origin) should be documented. Acquisition of cells, tissues, and organs are required to meet the defined standards of the American Association of Tissue Banks (AATB), specifically the registry of donors for tissues, record-keeping, labeling, product tracking, and notification of communicable disease transmission requirements (**1**, **2**). Ethical and legal practices should be observed, including the use of consent forms for the donation of human cells, tissues, and organs (**32**).

4.4.3 *Animal Sources*—Animal sources and screening is required to minimize potential cross-species transmission of known and zoonotic agents (**33**). Here, the required tests are dependent upon the donor species and geographical region. Xenotransplantation guidelines are applicable and the manufacturer is required to liaise with accredited testing laboratories with relevant experience, and with regulatory agencies to identify and validate appropriate test programs (**7**, **34**).

4.5 *Cell, Tissue and Organ Processing and Characterization*:

4.5.1 *Processing*—In relation to the design, specification, and fabrication of TEMPs, cGMPs in combination with the proposed Good Tissue Practices (GTP) must be implemented where appropriate by each TEMP manufacturer (**2**, **7**, **30**, **31**, **34**, **35**, **36**, **37**).

4.5.2 *Cells*—Guidelines on general principles of process validation are published by FDA's CDER and CDRH (**38**) and should be followed. The requirements for testing and the