



ACCREDITATION MANUAL – Standards for Musculoskeletal Tissues (Chapter J)

EUROPEAN GROUP FOR ACCREDITATION AND
LIAISON OF BLOOD-TISSUES AND CELLS ESTABLISHMENTS



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INTRODUCTION

EGALiTE is a voluntary accreditation programme endorsed by the leading European Scientific Societies [European Eye Bank Association (EEBA), European Association of Tissue and Cell Banks (EATCB), and European Society for Blood and Marrow Transplantation (EBMT), and European Blood Alliance (EBA)].

The EGALiTE Standards are designed to provide guidelines for organisations, programmes, facilities, and individuals involved in activities pertaining to Substances of Human Origin (SoHO) - or providing support services for such activities – and who wish to apply for the European/EGALiTE Accreditation Program.

These Standards are designed by experts in the SoHO field for facilities wishing to demonstrate their commitment to quality medical care and best laboratory practice through an EGALiTE accreditation.

EGALiTE Standards are intended to apply to all actions performed by SoHO Entities in the preparation of SoHO, which include donor recruitment, selection, evaluation, testing, and SoHO collection, sampling, quality control, processing, preservation, storage, release and distribution for clinical application. The standards applicable to hematopoietic progenitor cells (HPC) activities are defined by FACT-JACIE (Foundation for the Accreditation of Cellular Therapy and Joint Accreditation Committee of the International Society for Cell and Gene Therapy and the European Society for Blood and Marrow Transplantation (EBMT))^{*} and the World Marrow Donor Association (WMDA)[†], and are not included in this guide.

The EGALiTE Standards were defined taking into account on the good practices defined by:

- European Directorate for the Quality of Medicines & HealthCare of the Council of Europe (EDQM) Guide to the quality and safety of tissues and cells for human application¹;
- EDQM Guide to the preparation, use and quality assurance of Blood Components²
- FACT-JACIE³;
- WMDA Standards⁴
- EuroGTP I and EuroGTP II⁵
- And other guidelines, namely related with the Good Manufacturing Practices (GMP)⁶ and quality management.

^{*} The scope of the FACT-JACIE Standards includes:

- HPCs defined as self-renewing and/or multi-potent stem cells capable of maturation into any of the hematopoietic lineages, lineage-restricted pluripotent progenitor cells, and committed progenitor cells, regardless of tissue source (bone marrow, umbilical cord blood, peripheral blood, or other tissue source).
- Nucleated cells or mononuclear cells from any hematopoietic tissue source (marrow, peripheral blood, umbilical cord, and placental blood) collected for therapeutic use other than as HPCs.
- Immune effector cells (IECs), defined as cells, in vitro modified or not, that have differentiated into a form capable of modulating or effecting a specific immune response.
- Genetically modified cells, defined as cells that have been modified by replacing a disease-causing gene with a health copy of the gene, inactivating a disease-causing gene that is not functioning properly, or introducing a new or modified gene into the body to help treat a disease.
- Clinical administration of the cellular therapy products derived from umbilical cord.

[†] WMDA standards cover all aspects of blood stem cell registry operations

These Standards are not intended to establish absolute best practice or include all procedures and practices that an organisation, programme, facility, or individual should implement if the standard of practice in the community or applicable governmental laws or regulations have determined additional requirements. Each organisation, programme, facility, and individual should analyse its practices and procedures to ascertain whether additional standards apply. In addition, compliance with these Standards is not an exclusive means of complying with the required standards of care as dictated by local, national, or international laws or regulations.

Compliance with the Standards does not guarantee compliance with Applicable Law. Governmental regulations must also be followed. It is the responsibility of the individual facility to determine which laws and regulations are applicable. In some cases, regulations of governmental authorities outside of the jurisdiction of the Donation Centre may apply; for example, when a facility is sending or receiving SoHO from outside of its immediate jurisdiction.

Compliance with other organisations' standards or governmental regulations does not ensure that the Standards have been met. Governmental regulations supersede any organisation's standards if those regulations set a higher standard or are inconsistent with a specific standard. However, if a standard is more rigorous than a governmental regulation, that standard must be followed.

Disclaimer

EGALiTE expressly disclaims any responsibility for setting maximum standards and additionally expressly disclaims any responsibility, liability, or duty to member programmes, directors, staff, or programme donors or patients for any such liability arising out of injury or loss to any person by the failure of member programmes, directors, or staff to adhere to the Standards or related guidance.

While the EGALiTE Accreditation Programme encourages the sharing of best practices and recommendations, it does not assume the role of a regulatory body or authority. The EGALiTE Accreditation Programme involves a peer review process designed to assess and evaluate the compliance of SoHO organisations with standards and criteria established in the present document, where experts in the field conduct assessments based on predetermined criteria. The peer review process is conducted with the utmost independence and impartiality to ensure a fair and unbiased evaluation, and the compliance with the best practices.

The EGALiTE Accreditation Programme is not responsible for informing National Competent Authorities of any non-compliance identified during the peer review process, including major non-compliances.

Participants voluntarily engage in this process to demonstrate their commitment to quality and best practices, and organisations participate in the EGALiTE Accreditation Programme voluntarily, acknowledging that the outcomes of the process are not intended for regulatory purposes.

ABBREVIATIONS[‡]

ADM	Acellular dermal matrix (ADM)
AM	Amniotic Membrane
aW	available water
CAPA	Corrective and Preventive Actions
CFU	Colony-forming units
CMV	Cytomegalovirus
CV	Cardiovascular
DALK	Deep anterior lamellar keratoplasty
DCD	Deceased donors after circulatory death
DMEK	Descemet membrane endothelial keratoplasty
DMSO	Dimethyl sulphoxide
DSAEK	Descemet stripping automated endothelial keratoplasty
EATCB	European Association of Tissue and Cell Banks
EBA	European Blood Alliance
EBMT	European Society for Blood and Marrow Transplantation
EBV	Epstein–Barr virus
ECDC	European Centre for Disease Prevention and Control
EDQM Blood	Guide to the preparation, use and quality assurance of Blood Components (20 th Edition)
EDQM Guides	<i>Guide to the quality and safety of tissues and cells for human application</i> and <i>Guide to the preparation, use and quality assurance of Blood Components</i>
EDQM Tissue and Cells	Guide to the quality and safety of tissues and cells for human application (5 th Edition)
EDQM	European Directorate for the Quality of Medicines and Healthcare
EEBA	European Eye Bank Association
EK	Endothelial keratoplasty
EM	Electron microscopy
EU	European Union
EuroGTP II	Good Practices for demonstrating safety and quality through recipient follow-up - Good Practices for evaluating quality, safety and efficacy of novel tissue and cellular therapies and products (EU Project 709567)
FMEA	Failure mode and effects analysis
FMECA	Failure mode, effects and criticality analysis
FMT	faecal microbiota transplantation
FTSG	Full-thickness skin graft

[‡] For practical reasons, the present list includes the abbreviations and acronyms utilized in other chapters of the EGALiTE Standards.

GAPP JA	Facilitating the Authorisation of Preparation Process for blood, tissues and cells, Joint Action
GMP	Good Manufacturing Practice
HACCP	Hazard analysis and critical control points
HM	Human Milk
HMB	human milk bank
HoP	Holder pasteurisation
HV	Heart valve
IDM	infectious disease marker
JACIE	Joint Accreditation Committee of the ISCT (International Society for Cellular Therapy) and the EBMT
MiRCA	Microbiological Risk of Contamination Assessment tool for tissues and cells
MSK	Musculoskeletal Tissues
ORHA	Organisations for Human Application
PK	Penetrating keratoplasty
PPA	Preparation Process Authorisation
PQR	Product Quality Review
PRF	Platelet-Rich fibrin
PRP	Platelet-Rich Plasma
QM	Quality Manager
rCDI	<i>Clostridioides</i> (formerly <i>Clostridium</i>) <i>difficile</i> infection
RP	Responsible Person
SARE	Serious Adverse Reaction and Event
SED	Serum Eye Drops
SMF	Site Master File
SoHO	Substances of Human Origin
SOP	Standard Operating Procedure
TED	Tissue Establishment Dossier
TGOT	Technical Guidelines for Ocular Tissue
TNC	Total nucleated cell
UCB	Umbilical Cord Blood
URS	User-requirement specifications
VMP	Validation Master Plan
WMDA	World Marrow Donor Association

DEFINITIONS[§]

Audit	means a systematic and independent examination to determine whether activities and the related results of such activities comply with legislation and planned arrangements and whether such arrangements are applied effectively and are suitable to achieve the objectives ⁷
Collection	means a process by which SoHO are obtained from a person, including any preparatory steps, such as hormone treatment, needed to facilitate the process at, or under the supervision of, a SoHO entity ⁷
Donation Centre	A SoHO Entity that carries out one or more of the activities: SoHO donor history review and eligibility assessment; SoHO testing of donors for eligibility or matching purposes; collection of SoHO from donors or patients.
Donor recruitment	means any activity aimed at informing persons about activities related to SoHO donation or at encouraging them to donate SoHO ⁷
Must (or shall)	Indicates an absolute requirement. Compliance with the statement is mandatory, and failure to meet this requirement is considered a violation of the standard.
Processing	All operations involved in the preparation, manipulation, preservation, storage and packaging of SoHO intended for human application. ¹ means any operation involved in the handling of SoHO, including, but not limited to, washing, shaping, separation, decontamination, sterilisation, preservation and packaging, except for the preparatory handling of SoHO for immediate human application during a surgical intervention, without the SoHO being removed from the surgical field before they are applied ⁷ .
Qualification	According to European Union Good Manufacturing Practice (EU GMP) ^{6,8} , the action of proving that any equipment works correctly and actually leads to the expected results. More generally, qualification is applied to the inputs to a process, i.e. equipment, facilities, materials and software (and their suppliers), as well as to operators and the relevant written procedures ¹
Quality Management System	The organisational structure, with defined responsibilities, procedures, processes and resources, for implementing quality management, including all activities that contribute to quality, directly or indirectly ¹
Risk assessment	Identification of potential hazards with an estimation of the likelihood that they will cause harm and of the severity of the harm should it occur ¹ .

^{§ §} For practical reasons, the present list includes the definitions referred in other chapters of the EGALiTE Standards.

Should	Indicates a recommendation. While it is not mandatory, adherence to this statement is strongly advised to ensure the best outcomes. Non-compliance is not a violation of the standard but may affect the overall effectiveness or quality of the implementation.
SoHO Entity	Means an organisation legally established in the Union that carries out one or more of the SoHO activities that have a direct impact on the quality, safety or effectiveness of SoHO, as follows: (i) SoHO donor registration; (ii) SoHO donor history review and medical examination; (iii) testing of SoHO donors or of persons from whom SoHO are collected; (iv) collection; (v) processing; (vi) quality control; (vii) storage; (viii) release; (ix) distribution; (x) import; (xi) export; (xii) human application; (xiii) clinical-outcome registration. ⁷
SoHO establishment	means a SoHO entity that carries out any of the following SoHO activities: (a) both processing and storage; (b) release; (c) import; (d) export. ⁷
SoHO preparation	means a type of SoHO that: (a) has been subjected to processing and, where relevant, one or more other SoHO activities referred to in Article 2(1), point (c) of the EU SoHO Regulation; (b) has a specific clinical indication; and (c) is intended for human application to a SoHO recipient or is intended for distribution. ⁷
SoHO Regulation	Regulation (EU) 2024/1938 of the European Parliament and of the Council of 13 June 2024, on standards of quality and safety for substances of human origin intended for human application and repealing Directives 2002/98/EC and 2004/23/EC.
Substance of Human Origin (SoHO)	means any substance collected from the human body, whether it contains cells or not and whether those cells are living or not, including SoHO preparations resulting from the processing of such substance ⁷
Validation	Documented evidence giving a high degree of assurance that a specific process or system, including pieces of equipment or the environmental conditions, will perform consistently to deliver a product meeting its pre-determined specifications and quality attributes, based on intended use (EU Directive 2006/86/EC⁹)¹. or Confirmation, through the provision of objective evidence, that the requirements for a specific intended use or application have been fulfilled (ISO9000:2015¹⁰)¹
Verification	Preferred term for the validation or qualification of IT systems/software. Or, Confirmation, through the provision of objective evidence, that specified requirements have been fulfilled (ISO9000:2015 ¹⁰) ¹

INDEX/STANDARDS STRUCTURE

GENERIC STANDARDS FOR SoHO ACTIVITIES:	A. DONOR SELECTION & DONATION:	A.1. LIVING DONATION	F. OCULAR TISSUES
		A.2. DECEASED DONATION	G. AMNIOTIC MEMBRANE
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PART J.1.: MUSCULOSKELETAL TISSUES

Donor Evaluation

STANDARD:

J.1.001 The following age limits must be defined:

- a. for bone, the minimum age for both sexes is 6 years;
 - i. for non-structural grafts, no upper limit is applied;*
 - ii. for structural support, younger donors (age 15-55 years) are preferred;**
- b. for osteoarticular grafts, cartilage and menisci, the age range is 15-45 years;*
- c. for tendons and fascia lata, the recommended age range is 15-65 years.*

Explanation:

Critical quality attributes of MSK grafts may be affected by the donor's age and sex, and medical and lifestyle history.

Age limits may be revised, based on performance of a validation study.

Evidence:

Selection criteria is defined in a Standard Operating Procedure (SOP).

Random evaluation of collection reports may assist the evaluation of compliance. .

STANDARD:

J.1.002 Screening of donors of MSK tissue must be conducted for:

- a. diffuse connective-tissue disease which may reduce tissue quality;*
- b. metabolic bone diseases (severe osteoporosis, osteopetrosis, Paget disease etc.);*
- c. corticosteroid and bisphosphonate treatment (depending on doses and treatment duration);*
- d. evidence that the donor has ingested, or been otherwise exposed to toxic substances that could be transmitted in donated material in dosages that could endanger the health of recipients (e.g. cyanide or heavy metals such as mercury or gold);*
- e. significant local infection on potential donor site;*
- f. prior high radiation exposure at the location of the tissue to be donated;*
- g. evidence of trauma (e.g. open fracture) at the procurement site, or presence of joint deformities (evaluate the possibility of contraindication for osteochondral, structural bone and/or cartilage);*
- h. iatrogenic or degenerative tears or lesions detected during procurement of cartilage, menisci, tendons and osteoarticular grafts;*
- i. Lifestyle factors; poor nutritional status, diseases of the digestive system and excess alcohol consumption can impact on the quality of MSK grafts.*

Collection

STANDARD:

J.1.003 Staff must have the necessary anatomical knowledge to accurately obtain not only the regular tissues procured (femur, patellar ligaments etc.), but also specially requested materials (e.g. whole elbow).

Evidence:

Staff's CVs and any relevant registries of relevant training may provide useful evidences to assess this requirement. .

Example(s):

Staff qualification and continuous training may ensure that staff has enough knowledge to perform this activity

STANDARD:

J.1.004 The MSK procurement team for deceased donation must be composed of at least two (but preferably three) people.

Explanation:

The number of people involved in procurement should be determined in advance, depending on the amount of donated tissues per procurement procedure. To minimise the risk of contamination during procurement it is recommended to limit the maximum number of team members.

Evidence:

SOP defining the criteria to define the procurement team.

STANDARD:

J.1.005 Procurement team members must be gowned in sterile clothing and wear sterile gloves, face shields, glasses and protective masks, after surgical hand disinfection.

Evidence:

Procedures and techniques described in the SOP.

STANDARD:

J.1.006 The following steps for MSK procurement must be defined in dedicated SOP(s):

- a. Donor preparation*
- b. Donor draping*
- c. Tissue procurement*
- d. Microbiological control*
- e. Tissue packaging*
- f. Donor reconstruction*
- g. Procurement documentation*

Explanation:

Donor preparation: it includes washing, shaving and pre-operative disinfection of skin to reduce transient and resident microbial flora;

Donor draping: a local sterile field using disposable sterile drapes must be established before procurement to effectively reduce risk of microbial contamination;

Tissue procurement: all MSK tissues must be procured using an aseptic technique to decrease the risk of contamination. The following best practices can be applied:

- i. Personnel located at one side of the donor should not change to the other side until they have finished procuring all tissues from their own side, and surgical instruments should not be shared between personnel;
- ii. The packaging area should be isolated and separate from the operating field;
- iii. A fixed procurement sequence should be established, from 'cleanest' (e.g. lower limbs) to 'dirtiest' areas (e.g. abdominal cavity);
- iv. Gloves and surgical blade should be changed after the recovery of each tissue, or at least after the recovery of tissues in a specific area of the body (e.g. left leg) to avoid microbiological cross-contamination between tissue fragments of different zones.

Microbiological control: it is recommended to perform a microbiological control on each procured tissue. Such controls can be performed immediately after procurement or before commencement of processing to identify any initial microbiological growth. Sampling methods should be realised in conformity with the EDQM T&C Guide and defined in SOPs in conjunction with the microbiological laboratory in charge of analysis.

Tissue packaging: procured tissue must be inspected and identified appropriately before packaging and labelling to avoid mix-ups. MSK tissue must be packaged in a manner that minimises contamination risk, using a validated packaging system, to assure its isolation from the external environment

Evidence:

Procedures and techniques described in the SOP(s).

STANDARD:

J.1.007 Donor's body must be reconstructed to maintain its original anatomical appearance

Explanation:

Replica prosthesis approximating the size of the donated bone may be used to replace the procured bone. The subcutaneous tissue and skin should be sutured. The sutures should ensure no leakage can occur from the incision, and be cosmetically unobtrusive as possible. The use of materials and sutures suitable for cremation should be considered.

Evidence:

Procedures and techniques described in the SOP.

STANDARD:

J.1.008 When applicable, procurement from living donors follows the same basic requirements as for procurement of tissue from deceased donors

Explanation:

MSK tissue procured from living donors is likely to be procured by healthcare professionals whose primary role is not tissue donation. Therefore, it is important that these individuals be trained in the requirement to handle and package the grafts aseptically, and label the grafts and document the procedure appropriately

Evidence:

Procedures and techniques described in the SOP.

STANDARD:

J.1.009 After procurement: the tissues must be placed individually in a sterile and airtight packaging until they are transported to the tissue establishment

Explanation:

Each individual segment of tissues should be individually packaged in at least two sterilised packaging layers after procurement and placed in a container able to ensure storage at the required temperature. However, in cases where multiple segments of tissue are to be processed in the same batch, different tissues may be packaged together. In either case, individual pre-processing microbiological evaluation of each segment is mandatory.

Evidence:

Procedures and techniques described in the SOP.

STANDARD:

J.1.010 For the temporary storage and transportation to the tissue establishment, storage conditions, temperature and duration must consider whether maintenance of cell viability is crucial or not

Explanation:

Temperature and duration during temporary storage and transport must be validated.

Evidence:

SOP and validation reports (when applicable).

Example(s):

Tissues must be refrigerated between 2 and 8 °C for preferably not longer than 12 hours immediately after procurement to preserve viability, otherwise validated defined conditions (temperature and duration) should be used to ensure viability.

Depending on the further steps of the process, tissues can be temporarily stored in a dried state or placed in a transport solution buffered at a physiological pH with the possible addition of antibiotic cocktail, culture medium or preservation fluid (e.g. highly concentrated saline solution).

STANDARD:

J.1.011 All relevant information associated with the procurement of MSK tissues must be included in the procurement report, to be given to the Tissue Establishment

Explanation:

As a minimum, this report should contain the following information:

- a. description and identification of the procured material (specifying all procured tissues);
- b. any relevant morphological detail of procured tissues;
- c. presence of anatomical damage or abnormalities, including those introduced during procurement;
- d. Additional information may also be included, for example:
- e. non-procured standard tissues and the reason;
- b. traceability information about: equipment, reagents and disposal of material.

Evidence:

Associated form(s) and SOP(s)

Processing, preservation and storage

STANDARD:

J.1.012 All stages of tissue processing must take place within a controlled environment. Although classified cleanrooms are often not formally required for initial processing steps when validated sterilisation and virus-inactivation processes are applied subsequently, it is nevertheless necessary to control media quality (especially air and water) and to work with appropriately disinfected or sterilised equipment.

Explanation:

For terminally sterilised grafts, at a minimum, the packaging step after cleaning and/or disinfection, but before sterilisation, should be conducted in a qualified cleanroom; see European Union Good Manufacturing Practices (GMP) classification. The official requirements vary between jurisdictions, but EU GMP Grade C is usually specified (WHO TRS 823, 1992).

For non-terminally sterilised grafts, the requirements for the processing environment depend upon whether the national authority mandates conformity with the EU GMP guidelines, or whether different guidelines – e.g. the GTP (good tissue practice) guidelines – are applicable.

Tissues that are exposed to the environment without a subsequent microbial inactivation process must be processed in environments with an air quality equivalent to Grade A as defined in EU GMP.

Many national requirements are more stringent, requiring Grade B (EU GMP) as a background, which may be more appropriate for the processing of bone and tendons that are not followed by a terminal sterilisation step. Bone that is destined for terminal sterilisation can be processed in a Grade C environment

STANDARD:

J.1.013 Cleansing (physical preparation/defatting) must not be performed in the procurement site

Explanation:

Cleansing: The initial processing of bone and other MSK tissue generally involves mechanical steps that remove extraneous tissue. In the case of bone, residual muscle tissue and periosteum are resected, and cartilage may be debrided.

After procurement, MSK tissue allografts may undergo no processing prior to packaging and storage for transplantation, or be subjected to various types of physical and/or chemical downstream processing.

Evidence:

Procedures and techniques described in the SOP.

STANDARD:

J.1.014 Residue elimination should be achieved with physical treatments including centrifugation, ultrasound or high- pressure waterjet. Such process should demonstrate sufficient removal according to defined critical quality attributes.

Explanation:

Residual bone marrow, lipids and blood components in and/or on MSK tissue grafts can have a negative effect on subsequent processing and final graft quality. Such residues may increase the viable microbiological load, may have a negative effect on sterilisation processes and might be a cause of immunogenic reactions or delayed incorporation in graft recipients. They may also contain infectious agents derived from the donor. Such residual components should therefore be removed or depleted where possible. For this purpose, various treatments may be applied, such as chemical treatment able to dissolve or break up lipids and cells with organic solvents (e.g. acetone, chloroform, ethanol) or such as modulating osmolarity of aqueous solutions.

STANDARD:

J.1.015 Pooling of MSK tissue from two or more donors during processing must be avoided.

Explanation:

The only exception is where it is supported by a comprehensive risk–benefit assessment and it has been demonstrated to be the only way of providing sufficient clinically effective tissues or cells. If performed, traceability must be fully ensured.

STANDARD:

J.1.016 Any claim of inactivation or elimination of micro- organisms (virus, bacteria, spores, fungi) must be validated using organisms typically found in the tissue, model organisms representative of their type or ideally a “worst case” organism known to be highly resistant to the method in question.

Explanation:

Sterilisation and disinfection processes for MSK grafts are applied to minimise the risk of transmission of microbiological agents. They may be applied before, during or after any processing procedure and must be validated.

Evidence:

Associated SOPs and validation reports.

STANDARD:

J.1.017 Proof of sterility can be obtained by performing microbiological tests on tissue samples or by parametric release based on confirmed application of a minimum level of sterilisation

Evidence:

Associated SOPs.

Example(s):

Application of a minimum level of sterilisation: Achieving a certain core temperature for a defined period, or a defined dose of irradiation

STANDARD:

J.1.018 Cancellous/corticocancellous bone must comply with the following critical proprieties:

- *Cancellous bone free of muscle, periosteum and cortical bone.*

- *Corticocancellous bone free of muscle. Cartilage can be preserved or removed in the case of geometrical pieces if necessary (femoral head, femoral condyle, tibial plateau ...)*
- *Reduction or removal of fat, blood cells and bone marrow*
- *Absence of microbiological growth after processing*
- *Adequate size and volume*
- *For geometrical pieces supporting load constraints: the essential native biomechanical properties of the bone must not be significantly altered (including terminal sterilisation if applied)*
- *Absence of cytotoxicity due to the processing protocol*
- *In cases of dehydration (freeze drying) a residual moisture of 1-6 % (w/w) or available water (aW) of < 0.5*

STANDARD:

J.1.019 Cortical bone grafts must comply with the following critical proprieties:

- *Free of muscle, periosteum and cancellous bone*
- *Reduction or removal of fat, blood cells and bone marrow*
- *Absence of microbiological growth after processing-*
- *Adequate size and volume*
- *For grafts supporting load constraints: the essential native biomechanical properties of the bone must not be significantly altered*
- *Absence of cytotoxicity due to the processing protocol • In cases of lyophilisation (freeze drying) a residual moisture of 1-6 % (w/w) or available water (aW) of < 0.5*

STANDARD:

J.1.020 Structural bones must comply with the following critical proprieties:

- *Free of periosteum. Ligament and muscular attachments as well as cartilage can be preserved if applicable*
- *Absence of microbiological growth after processing*
- *No morphology alterations (i.e. deformities, fracture callus ...)*
- *Absence of significant alteration of the native biomechanical properties (including terminal sterilisation if applied)*
- *Absence of cytotoxicity due to the processing protocol*

STANDARD:

J.1.021 Meniscus must comply with the following critical proprieties:

- *Absence of meniscal surgery antecedent on medical history*
- *Absence of blood straining and degenerative or traumatic lesions*
- *Absence of microbiological growth after processing*
- *Absence of significant alteration of the native biomechanical properties of meniscus (including terminal sterilisation if applied)*
- *Processing steps must largely reduce or remove fat, blood cells and bone marrow from bone block if applicable*
- *Absence of cytotoxicity due to the processing protocol*
- *Donor–recipient matching: meniscus dimensions (recommended) or donor–recipient height/weight*

STANDARD:

J.1.022 Tendons must comply with the following critical proprieties:

- *Absence of tendinous pathology antecedent on medical history*

- *Absence of muscle and peritendon*
- *Absence of blood staining, fibre separation, stiffness and degenerative or traumatic lesions*
- *Absence of microbiological growth after processing*
- *Absence of significant alteration of the native biomechanical properties (including terminal sterilisation if applied)*
- *Processing steps must largely reduce or remove fat, blood cells and bone marrow from bone block, if applicable*
- *Absence of cytotoxicity due to the processing protocol*

STANDARD:

J.1.023 Osteochondral allografts must comply with the following critical proprieties:

- *Absence of chondral pathology antecedent on medical history*
- *Absence of blood staining and degenerative or traumatic lesions*
- *Absence of microbiological growth at the time of distribution (depends on shelf life, which is determined by preservation method)*
- *Preservation of ≥ 70 % of viable chondrocytes (through validation)*
- *Donor–recipient matching: either graft dimensions (recommended) or donor–recipient height/weight*

STANDARD:

J.1.024 Demineralised bone matrix must comply with the following critical proprieties:

- *Free of muscle, periosteum and cartilage*
- *Reduction or removal of fat, blood cells and bone marrow*
- *Absence of microbiological growth after processing*
- *Calcium content ≤ 5 %*
- *Osteoinductive capability*
- *Adequate size and volume*
- *Absence of cytotoxicity due to the processing protocol*
- *Residual moisture of 1-6 % (w/w) or available water (aW) of < 0.5*

STANDARD:

J.1.025 Different preservation methods of MSK tissues, require different conditions and storage temperatures:

- *Frozen: -40 to -15*
- *Deep frozen: -80 to -60*
- *Cryopreserved: -196 to -140*
- *Dehydrated and freeze-dried: $+4$ to $+30$*
- *Fresh (hypothermic): $+2$ to $+8$*
- *Organ culture: 28 to 37*

Explanation:

Different preservation methods of MSK tissues, require different storage temperatures. These methods must be developed and validated to maintain the biological properties of tissues for long periods of time, from processing to distribution for transplant.

Refer to the EDQM T&C Guide for additional details

Evidence:

Associated SOPs and validation reports

STANDARD:

J.1.026 The shelf life of the tissue when kept at the designated storage temperature, which is dependent upon the packaging system (to guarantee the integrity and sterility of the graft) and the storage methods used, must be specified on the final label, and supported by validation data or a documented risk assessment

STANDARD:

J.1.027 MSK tissues be at least double-packed separately in pouches or in sterile sealed containers to avoid microbiological contamination and labelled immediately

STANDARD:

J.1.028 The material used for the packaging must be validated for use at the designated storage temperature, and shown to maintain its integrity during worst-case storage and transport conditions.

The absence of adverse effects of packaging material on tissue must be supported by a documented risk assessment or validation data.

Example(s):

Consideration should be given to the risk that components of the packaging material, for example plasticisers, may contaminate the tissue.

Quality Controls

STANDARD:

J.1.029 Quality-control tests on MSK grafts must take at least the following quality criteria into account:

- a. morphology and integrity of the MSK grafts;*
- b. shape and size of the graft;*
- c. residual moisture or available water in lyophilised or dehydrated grafts*
- d. osteo-inductive activity (in vivo or in vitro) in demineralised bone;*
- e. sterilisation indicators;*
- f. no evidence of microbiological growth.*

Explanation:

Shape and size of the graft: especially for certain types of graft, for example meniscal cartilage, which require close size matching between the donor and recipient; the relevant measurements should be made using calibrated instruments when all physical processing has been completed;

Residual moisture or available water in lyophilised or dehydrated grafts: the minimum and the maximum level to be defined according to validation studies

STANDARD:

J.1.030 During procurement or before processing, microbiological samples must be collected to establish the initial contamination to assist in making a decision during quarantine regarding the release of procured material for further processing.

Explanation:

The inactivation capacity of manufacturing processes (e.g. disinfection, sterilisation) should be taken into account.

Samples for microbiological testing should also be collected before or during packaging of the final product. Possible sampling techniques for microbiological testing include:

1. swabs;
2. destructive methods (e.g. biopsy or sacrificing a proportion of ground tissue);
3. collection of the last portion of the fluid used for washing of the tissue graft for subsequent analysis, usually following filtration.

STANDARD:

- J.1.031 The result of the microbiological control before final release must be negative.
If a positive microbiology result is obtained, the tissue must be discarded or sterilised with a validated method taking into account the nature and level of the microbial bioburden.*

Explanation:

Depending on the micro-organism found, a risk-assessment analysis should be done to assess the suitability of the other MSK tissues from the same donor.

Refer to the EDQM T&C Guide for the list of micro-organisms that if identified in pre-processing tissue or cell samples should result in discard of tissues and cells.

Evidence:

Risk Assessment report(s) and associated SOP.

Example(s):

A risk assessment including the potency of any sterilisation processes employed, and the clinical relevance of the micro-organism, should be done to analyse the suitability of the rest of the MSK tissue from same donor.

Distribution

STANDARD:

- J.1.032 The follow transportation systems must be used, depending on the preservation method used:*
- a. Frozen and deep-frozen grafts can be carried using a container with dry ice or qualified cooling system.*
 - b. Cryopreserved grafts can be carried using dry-shipping containers (vapour-phase nitrogen < -140 °C).*
 - c. Dehydrated and freeze-dried grafts can be carried using a container sufficient to protect the integrity of the packaging system;*
 - d. Fresh grafts can be carried using a container that ensures the defined storage temperature*

Explanation:

Frozen and deep-frozen grafts: Once the graft has been thawed, it cannot be re-frozen;

Cryopreserved: If dry ice is used for transportation of the MSK allograft, the tissue should not be returned to liquid or vapour-phase nitrogen tanks unless validated or supported by a documented scientific rationale. Once the graft has been thawed, it cannot be re-frozen.

STANDARD:

- J.1.033 Storage containers with tamper-evident seals must be used*

STANDARD:

- J.1.034 Instructions for thawing frozen, deep frozen or cryopreserved grafts, or for rehydrating dehydrated grafts, must be established and validated by the SoHO Establishment before the clinical use.*

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