



ACCREDITATION MANUAL

Generic Standards for SoHO Activities

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



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Contents

INTRODUCTION.....	1
ABBREVIATIONS.....	4
DEFINITIONS	6
INDEX/STANDARDS STRUCTURE.....	8
PART 00: GENERIC STANDARDS FOR SoHO ACTIVITIES	9
General.....	9
Ethical issues	10
Quality Management	11
Risk Management and Risk Assessment	14
Qualification, Validation and Verification.....	16
Personnel and organisation	19
Premises.....	23
Equipment and Material	24
Outsourced Activities Management	27
Documentation and Records	27
Packaging and Labelling.....	32
Continuity Planning.....	34
PART A: DONOR SELECTION & DONATION PROCEDURES	35
Donation Centres	35
Donor Evaluation	36
Donor Testing.....	38
Transport & Shipping to SoHO Establishment	42
PART A.1: LIVING DONATION.....	44
Evaluation of Living Donors	44
Living Donor Testing	45
PART A.2: DECEASED DONATION.....	46
Evaluation of Deceased Donors	46
Deceased Donor Testing	46
PART B: COLLECTION	48
Equipment and Materials	49

Identification, packaging, containers and labelling	50
Collection Procedures	51
PART C. PROCESSING, STORAGE AND RELEASE OF SoHO	56
Receipt at the SoHO establishment	56
Donor Testing and results' reporting	57
Processing Facilities	58
Processing Activities	61
Processing Reagents	63
Coding, Labelling and packaging	65
Quality Controls	66
Significant changes in processing protocols	66
Packaging and Storage activities	67
Storage Facilities	68
PART D. DISTRIBUTION	73
Transport after release	73
PART E. REGISTRIES AND VIGILANCE	77
Clinical Investigations and Biovigilance	77
BIBLIOGRAPHY	79

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
	B. COLLECTION		H. SKIN
	C. PROCESSING, STORAGE AND RELEASE OF SoHO		I. CARDIOVASCULAR
			J. MUSCULOSKELETAL
	D. DISTRIBUTION		K. UMBILICAL CORD BLOOD
			L. ADIPOSE TISSUE
	E. REGISTRIES AND VIGILANCE		M. HUMAN MILK
			N. BLOOD COMPONENTS FOR TOPICAL USE OR INJECTION
			O. INTESTINAL MICROBIOTA

PART 00: GENERIC STANDARDS FOR SoHO ACTIVITIES

General

STANDARD:

00.001 The SoHO Entity must abide by Applicable Law.

The SoHO Entity must be licensed, registered, or accredited as required by the appropriate governmental authorities for the activities performed

Explanation:

Applicable Law may require registration or certification with the Member State/Competent Authority or may require accreditation from professional societies for the activities performed within the SoHO Entity. (Any term used in this requirement is referred to the authorization level and not referred to any certification program unless the accreditation is recognized as for authorization purposes in any case)

Evidence:

While observing facilities and processes, auditors will note if there are apparent practices that are not in compliance with Applicable Law. Evidence of compliance with the Standards will require pre-audit information identifying prevailing governmental authorities, and documentation of certificates, permits, or licenses.

Documentation of registration with the relevant governmental authorities will be sent to the EGALITE office with the accreditation application materials. The auditor may ask to see it on site. A copy may not be immediately available, however, the Responsible Person (RP) should know who in the institution is responsible for the registration, and where a copy may be obtained. It is not appropriate to request a faxed copy from the regulatory authority during the on-site audit.

In the EU Blood, Tissues and Cells fall under a common 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”.⁷

Furthermore, individual Member States in the EU may add additional directions to the EU legislation that also must be followed. Member State-specific regulations will not be detailed here.

Example(s):

In the EU, the competent authorities in the individual Member States shall safeguard that all SoHO establishments have been accredited, designated, authorized, or licensed and that these establishments have implemented the EU SoHO Regulation and/or other national regulations.

Examples of verified compliance with regulations include hospital accreditation (such as the Joint Commission), state licensure, licensing of SoHO establishments by the Member State in the EU, and any other applicable accreditation body required at national/regional level.

STANDARD:

00.002 A sufficient number of procedures to be able to show evidence of compliance with the different standards, must have been performed in the twelve (12) month period immediately preceding accreditation or re-accreditation.

Explanation:

This Standard refers specifically to the number of procedures performed by the SoHO Entity.

The number of procedures should be determined based on a justified, sustained and documented assessment performed by the SoHO Entity.

It may include the procedures performed in the context of validation(s) of new or modified procedures.

It aims to ensure the compliance of all technical requirements and all Standard Operating Procedures (SOPs) defined by the SoHO Entity for the collection, preparation, preservation and/or distribution, and should address any risks to integrity of the SoHO or risks to recipient and donors' safety

Evidence:

A review of current SoHO Entity reports (i.e. Product Quality Review (PQR), validations and/or statistical data/process control) can be used to ascertain whether the SoHO Entity has complied with the required number of procedures.

The suitable number of procedures should be determined by the auditor, based on the evidence presented and the analysis of the results (e.g. Validation studies) presented.

Example(s):

For example, in the standards related to validation, sufficient processes must have been carried out to be able to document an adequate validation of a certain procedure.

To demonstrate compliance with respect to personnel training, sufficient processes must have been carried out to demonstrate such training. In the context of non-conformities management or corrective and preventive actions (CAPA) system, enough processes must have been carried out so that this system has evidence of functioning.

Ethical issues

STANDARD:

00.003 SoHO Entity must operate on a non-profit basis. SoHO should be supplied on an operational cost basis and no payment should ever exceed the justifiable fee for the services rendered

Explanation:

The principle of financial neutrality - meaning that no financial gain or loss will be incurred by the SoHO entity – should be ensured.

SoHO Entities can claim a reasonable amount to cover expenses but should not quote an unfair amount greater than the actual cost in order to make profits.

When calculating the operational costs of a SoHO Entity, which may have a variety of funding sources, consideration should be given to the long-term sustainability of the SoHO Entity. In order to do this, it is important to analyse the clinical need (for the different types of SoHO that the SoHO establishment will be processing and distributing) and to efficiently manage the SoHO establishment's 'value chain', which includes the costs of collection/ procurement, processing, storage, distribution, personnel, transport, infrastructure and administration, and the need to incorporate and maintain state-of-the-art processes and equipment, among others.

Evidence:

SoHO Entity mission and policies will be assessed during audit.

Ideally, SoHO Entity shall be able to evidence the rationale used in the estimation of costs of a specific SoHO.

Example(s):

Practical example of cost estimation for a service (ex: SoHO collection) or SoHO distributed by the SoHO entity

STANDARD:

00.004 The identity of the donor and recipient must be kept confidential (this standard does not apply for directed/related donations).

Explanation:

Such precautions will prevent abuse and protect the families of donors and recipients from feelings of anxiety associated with emotional involvement, obligation to return favours or guilt.

Evidence:

Auditors should review the procedures and system(s) implemented by the SoHO Entity to anonymise donors and recipients.

STANDARD:

00.005 The organisation and execution of activities based on donation and human application, as well as their clinical results, must be transparent and open to inspection, while ensuring that the personal anonymity and privacy of donors and recipients are protected (where pertinent and required by law).

Explanation:

Transparency can be achieved by maintaining public access to regularly updated comprehensive data on processes, in particular to data on donation and banking activities, allocation, distribution and import/export, demand for SoHO, human applications and the outcomes for recipients, and living donors, as well as data on organisation.

Evidence:

Auditors should review the procedures and policies in place.

STANDARD:

00.006 The allocation of SoHO must be guided by pre-defined criteria and ethical norms, not financial or other considerations. When applicable, allocation rules, defined by appropriately constituted procedures, must be equitable and based on clinical need, and/or externally justified and transparent parameters

Explanation:

Except in the case of direct donations, SoHO must be allocated among patients only in conformity with transparent and justifiable criteria and based on equitability and clinical needs.

SoHO Entity should have a SOP to provide consistent criteria for the allocation and distribution of their SoHO in compliance with applicable regulations. The established documented system of allocation and distribution should be ethical, fair and transparent for all patients served by the SoHO Entity. Access to SoHO should be provided without regard to recipient sex, age, religion, creed, skin, ethnic group or nation, unless warranted by donor/recipient compatibility or logistical factors. Emergency patients shall take priority over scheduled cases.

Evidence:

Auditors will review the policies and defined criteria and or registries/waiting lists (when applicable) implemented by the SoHO Entities.

Quality Management

STANDARD:

00.007 A SoHO Entity must implement a Quality Management System that covers the scope of all of its activities

Explanation:

The quality system must be designed to assure the quality and safety of SoHO donated/processed/distributed, as well as to ensure donor and staff safety and end-user service. This strategy requires the development of clear policies, objectives and responsibilities. It also requires implementation, by means of quality planning, quality control, quality assurance and quality improvement, to ensure the quality and safety of SoHO, and to provide end-user satisfaction

Each SoHO Entity must develop and maintain a quality system which facilitates meeting all the relevant minimum requirements identified in the SoHO Regulation⁷ and EDQM Guides, and which is based on the principles of good practice defined in the current standards, incorporating quality risk management and taking into account the relevant elements of EU GMP as in Directive 2001/83/ EC, when applicable.

To achieve this quality objective in a consistently good or correct manner, there must be a comprehensive, well-designed and correctly implemented quality system incorporating good practice and quality risk management.

Evidence:

A SoHO Entity must be able to demonstrate the existence of a document such as tissue establishment dossier (TED), Quality Manual or Site Master File (SMF), describing the full scope of activities.

A systematic approach to quality management must be implemented and maintained throughout all processes that influence the quality of SoHO.

STANDARD:

00.008 The quality system must ensure that all critical processes are specified in appropriate procedures and/or instructions and are carried out in accordance with the standards and specifications of good practice and that they comply with appropriate regulations and standards.

Explanation:

The quality system encompasses quality management, quality assurance, continuous quality improvement, personnel, premises and equipment, documentation, donation, collection/procurement, testing and processing, storage, release for circulation including distribution, quality control, change control, traceability, SoHO recall, external and internal auditing, contract management, validation, verification and qualification, and self-audit. The design of the system should incorporate appropriate risk management principles, including the use of appropriate tools.

STANDARD:

00.009 There must be a process in place that results in clearly defined and effective documentation that controls the modification of records and registers the approval of SOPs for all activities for which accreditation is sought

STANDARD:

00.010 A general policy regarding qualification of facilities and equipment, as well as validation or verification of processes, automated systems and laboratory tests, must be in place.

Explanation:

The formal objective of qualification, validation or verification is to ensure compliance with the intended use based on regulatory requirements.

Evidence:

Validation Master Plan (VMP), outlining the principles involved in the qualification of a facility and equipment, and defining the scope, validation policy, risk assessment, areas and systems to be validated, and relevant documentation for achieving and maintaining a qualified facility

STANDARD:

00.011 Personnel in responsible positions must have adequate authority to carry out their responsibilities. Their duties may be delegated to designated deputies of a satisfactory qualification level. There must be no gaps or unexplained overlaps in the responsibilities of those personnel concerned with the application of good practice.

Explanation:

Management has the ultimate responsibility to determine and provide adequate and appropriate resources (human, financial, materials, facilities and equipment) to implement and maintain the QMS and continually improve its suitability and effectiveness through participation in management reviews.

The responsibilities placed on any one individual should not be so extensive as to present any risk to quality.

Example(s):

Organigram(s) and descriptions of the roles, responsibilities, and tasks of personnel

STANDARD:

00.012 Training related to the individual technical work must be provided for all personnel whose duties take them into processing areas or into laboratories (including technical, maintenance and cleaning personnel).

Evidence:

Training registries should be observed to determine the compliance of this requirement.

STANDARD:

00.013 There must be written policies and procedures to describe the approach to training, including a record of training that has taken place, its contents and an assessment of its effectiveness

Explanation:

All personnel must receive initial and continuous training appropriate to their specific tasks. Training records must be maintained. Training programmes must be in place and must include the principles of good practice.

Example(s): Entities may provide registries of post-training evaluations to document their effectiveness. (e.g. registry of x number of a certain procedure correctly performed by the operator during training)

STANDARD:

00.014 Procedures must be in place for notifying the RP in a timely manner of any significant deviations, non-compliance with regulatory commitments, SoHO defects, or testing errors and related actions. Adequate resources should be made available for the timely resolution of deviations

STANDARD:

00.015 The investigation of deviations must include an assessment of component impact, including a review and evaluation of relevant operational documentation and an assessment of deviations from specified procedures. Deviations should be categorised depending on how critical they are to the quality and safety of SoHO, and how frequently they occur.

Explanation:

If it is determined that deviations could recur and/or there is doubt about compliance with quality and safety requirements, based on the estimated frequency of occurrence and severity (e.g. risk matrix) of the deviations, a root cause analysis should be performed to identify the underlying cause or causes of the deviation. This can be determined using quality risk-management principles. In cases where the true root cause(s) of the issue cannot be determined, consideration should be given to identifying and addressing the most likely root cause(s).

STANDARD:

00.016 An associated system for the implementation and monitoring of CAPA must be in place.

Explanation:

Appropriate CAPAs should be identified and taken in response to investigations, with a view to ensuring that existing problems affecting quality are identified and corrected, and that recurrence of the problem is prevented.

The need to consider a recall of SoHO or the need to quarantine materials should also be considered. CAPAs must be completed in a timely and effective manner.

The effectiveness of CAPAs should be monitored and assessed, in line with quality risk-management principles.

The systems in place for the management of deviations should be linked, where appropriate, to the systems in place for the management of SAREs.

Data relating to deviations should be routinely analysed to identify problems affecting quality that may require corrective action, or to identify trends that may require preventive action.

STANDARD:

00.017 Regular process quality reviews should be conducted with the objective of verifying the consistency of the existing preparation process and the appropriateness of current specifications for all starting materials (including SoHO) and for processed SoHO, as well as highlighting trends and identifying improvements which may be required.

Explanation:

A review should normally be conducted annually, taking into account the conclusions of previous reviews; it should be documented and include all SoHO which are imported, exported or intended for use in the manufacture of other products. Quality reviews may be grouped by SoHO type, where scientifically justified. A quality review of SoHO that are ready for circulation/release may also be considered as an instrument for surveying the overall quality status of SoHO processing, including collection.

Evidence:

The results of process quality reviews should be evaluated, and an assessment should be made whether any CAPA or any revalidation or re-verification should be undertaken.

Reasons for any such CAPA should be documented.

Risk Management and Risk Assessment

STANDARD:

00.018 A SoHO Entity must perform a comprehensive risk assessment of all its activities

Explanation:

A risk-based approach must provide justification for choices made throughout the design and implementation of processes with impact for the quality and safety of SoHO.

Risk assessment should refer to current scientific knowledge, should involve appropriate technical expertise and should be related to the protection of the patient and the donor.

This exercise allows the identification of those steps where most of the quality system controls are required and where validation of procedures is necessary.

Risk-mapping methodology is one of the risk-management tools. This methodology offers a visualised, comprehensive view of the likelihood and impact of an organisation's risks.

Risk assessment should include an estimation of the severity of any identified hazard (potential source of harm) and an estimation of the probability that the hazard will result in harm. Probability should be based on evidence and experience

Example(s):

A 'process flow' diagram listing all relevant steps, processes, reagents, tests and equipment can form the basis for the risk assessment exercise.

Numerous risk analysis methods, such as Fault tree analysis (FTA), Failure mode effect analysis (FMEA), Hazard analysis and critical control points (HACCP) or Failure mode effect and criticality analysis (FMECA), have been proven successful in a variety of applications.

The EDQM have developed a methodology specifically to assess aseptic risks in collection and processing of SoHO: Microbiological Risk of Contamination Assessment tool for tissues and cells (MiRCA)

STANDARD:

00.019 A periodic review mechanism must be implemented proportionally to the level of risk and considering new knowledge and potential inputs from inspection, internal audits or unexpected events

Explanation:

Risk assessment should be repeated and documented whenever a critical process is changed as part of a change-control process. Actions to mitigate any significant new risks, including validation, should be completed before any change is implemented.

Any evaluation of the risk to quality should be based on scientific knowledge, experience with the process and, ultimately, protection of the donor and recipient/patient.

The level of effort, formality and documentation of the quality risk-management process should be commensurate with the level of risk.

Example(s):

The approach to risk assessment should be systematic and should be documented. The most commonly applied risk-assessment methods are Hazard analysis and critical control points (HACCP), Failure mode and effects analysis (FMEA), Failure mode, effects and criticality analysis (FMECA), risk mapping and EuroGTP II tool.

STANDARD:

00.020 The policy and process for planning, executing and recording validation must be documented in written procedures.

Explanation:

This documentation may be assembled into a VMP. The VMP will typically include the following:

- validation policy,
- organisational structure of validation activities,
- summary of facilities, systems, equipment and processes to be validated,
- documentation format,
- planning and scheduling,
- change control,
- reference to existing documents.

STANDARD:

00.021 Whenever a novel process is implemented, or an existing process revised, it is incumbent on a SoHO Establishment to assess the efficacy and risk resulting from this change. It is recommended the use of the EuroGTP II methodologies, in order to perform a structured and systematic assessment, which enables SoHO Establishments to identify, quantify and mitigate risks associated with introducing novel procedures, and changes to existing ones.

Evidence:

Risk assessment report(s) issued by the EuroGTP II guidance and Interactive Tool ([Blood](#), [Tissues and Cells](#)), may be considered an evidence of compliance of this requirement.

Qualification, Validation and Verification

STANDARD:

00.022 The qualification, validation and verification of premises, equipment, materials, consumables, reagents and personnel must be ensured.

Explanation:

All critical aspects of the establishment's operations are sufficiently under control to provide continual assurance that SoHO will remain safe for patients and fit for purpose.

Validation is usually split into two components: qualification and validation (or verification)

The term 'qualification' is applied to each part of the process and to individual items, including cleanroom facilities, equipment, computer systems, materials and operators.

Such items should be qualified before they are first used in a process and then re-qualified at predetermined intervals, or when significant changes are made. Each individual item should be qualified separately to demonstrate consistent performance.

The critical aspects subject to validation, verification and qualification include:

- a. the facilities and equipment used in collection/procurement, processing, storage, testing and distribution, and any equipment and software used to manage their operation and data,
- b. materials and reagents that come into contact with SoHO,
- c. labelling and tracking materials, equipment and software,
- d. operational staff and the written procedures that instruct their work,
- e. process stages from collection/procurement to distribution where there is a risk of a detrimental effect on the quality and safety characteristics of SoHO if not performed correctly, based notably on the risk mapping tool,
- f. analytical test methods used to assess and confirm the safety and quality of donors, donations, and SoHO
- g. other auxiliary processes such as the transport and cleaning processes

Evidence:

A general policy regarding qualification of facilities and equipment, as well as validation or verification of processes, automated systems and laboratory tests, must be in place. The formal objective of qualification, validation or verification is to ensure compliance with the intended use and regulatory requirements

STANDARD:

00.023 There must be a VMP in place for every critical aspect of a SoHO Entity's activities.

Explanation:

The validation, verification and qualification policy should consider a process design phase where proficient knowledge of the process is achieved.

The test methods to be used and the acceptance criteria should be documented and approved by the establishment management before qualification or validation, or verification commences.

The key elements of the site qualification and validation programme should be clearly defined and documented in a validation master plan (VMP) or equivalent document.

Example(s):

When revalidation is based on quality control results or statistical data, this should be mentioned in the VMP

STANDARD:

00.024 It must be clear through documentation and/or status labelling which processes and items have been validated, qualified or verified and which are undergoing validation, verification or qualification

Explanation:

There should be a procedure that describes the management of these processes under validation, to guarantee the separation from validated processes.

Example(s):

The VMP or equivalent records should keep the status of validation for all critical processes.

STANDARD:

00.025 Verification or validation of analytical tests - the validation plan must take into account the variety of sample types and analyses to be tested, as there may be substances present that interfere.

Explanation:

In-house developed analytical methods should be validated.

Evidence:

Example(s):

The *Technical Annex 2 to overall GAPP guidance: assessing the quality and safety of donor testing, pathogen reduction and sterilisation steps as part of Preparation Process Authorisation (PPA)* may be considered a reference for analytical assays.

The European Pharmacopeia¹¹ may be used as standards for the definition of analytical assays.

STANDARD:

00.026 Computer Software and automated systems controlled by bespoke must be qualified and the verification of computerised systems must be commensurate with level of risk, intended use and potential implications of malfunction to quality and safety.

Explanation:

The level of qualification required for computerised systems is dependent on the criticality of the systems to the quality and safety of the SoHO. Therefore, a criticality rating based on a risk assessment should be applied to all computerised systems in place. The method of verification of these critical systems depends on the type/category of software used.

The design of, and changes to, software can have a significant impact on the quality and safety of SoHO and the integrity of critical data.

Risk assessment within the change control procedure will tell us the extension of the tests. It is therefore essential to maintain effective version control over software in use and to qualify new software and requalify existing software when changes are made. Establishments should be aware of the current version of software operating their relevant computer and automated systems at all times and should not allow upgrades of existing software by system suppliers without their approval.

Evidence:

Verification documents and/or internal verification of the results of tests undertaken and approved by the supplier/vendor or developer of the system can be considered evidence of compliance.

Software requirements should be included in the appropriate URS for the system they control

Example(s):

A set of documentation that is as detailed as necessary to ensure appropriate operation of the system must be in place.

STANDARD:

00.027 Internal and external audits must be scheduled and conducted in an independent manner by designated, trained and competent persons/organisations

Explanation:

Internal audits are normally carried out by the organisation's quality assurance personnel or can be done by a mandated person from outside (for example, quality assurance personnel from another SoHO Entity) with the help of internal personnel or by trained internal staff independently of their own department.

External audits are undertaken by external entities (namely expert bodies or cooperative parties) and are required for certification, authorization and accreditation purposes. External audits provide an opportunity for critical review by experts unfamiliar with the systems in place locally.

All audits should be documented and recorded.

Clear procedures are required to ensure that the agreed CAPA are undertaken appropriately. These actions and the evaluation of their effectiveness should be recorded

STANDARD:

00.028 Monitoring plan must be developed and implemented.

Explanation:

The plan should take into account the criticality of the premises, system or equipment, and should outline monitoring, user notification and mechanisms for problem resolution.

If an anomalous event is observed, personnel should follow the standard response described in the monitoring plan.

The standard response should involve notifying affected personnel and, if possible, initiation of a resolution response to the event and risk assessment of the affected SoHO. Depending on the severity of the problem and the criticality of the system or piece of equipment, a back-up plan may need to be implemented to keep the process or system operating.

STANDARD:

00.029 Qualification of materials and suppliers: A detailed user-requirement specifications (URS) must be available for materials

Explanation:

Before introducing a new critical material into a process, it should be qualified. This will involve confirmation that it meets the URS through examination of the material and of test data either from the manufacturer (Certificate of Analysis), a third party or in-house testing.

STANDARD:

00.030 Facilities and equipment must be qualified before use and when any significant change is implemented.

Explanation:

Facilities and equipment should be qualified following the four steps - Design qualification, Installation qualification, Operational qualification, Performance qualification. The extension of the qualification should be determined through a risk assessment exercise. Some steps might be executed together.

STANDARD:

00.032 All equipment or systems with a critical measurement function must be calibrated according to a planned schedule.

Explanation:

In practice, the measurement result of each piece of critical measuring equipment or system should be traceable through a documented and unbroken chain of calibrations back to the International System of Units

or to a recognised standard. The uncertainty of measurement should be established and quoted with subsequent results. Hence, the critical measuring equipment or system is compared against a standard; the standard is compared against a higher standard; and the chain is documented through calibration certificates.

Evidence:

If calibration is carried out by a third party, a copy of the calibration certificate for the specific measuring equipment or system used should be provided together with the calibration report.

Personnel and organisation

STANDARD:

00.033 Personnel must be available in sufficient numbers and with the necessary qualifications and experience to carry out the activities related to the donation, collection/procurement, testing, processing, storage and release for circulation (including distribution) of SoHO for human application and they must be trained and assessed as competent to perform their tasks.

Explanation:

There must be sufficient, suitably qualified personnel to carry out all tasks in compliance with quality and safety requirements.

This standard requires that it has to be an adequate number of trained personnel available for the SoHO Entity relative to the workload. The number of staff available and other responsibilities of the staff will vary from institution to institution based on the size and scope of the SoHO Entity, and no specific numbers of staff members are required by the Standards.

A designated back-up, trained individual is required, but this does not require the SoHO entity to hire an additional employee. There are many options to train personnel from other departments who are qualified to perform the necessary tasks should they be needed.

The RP should indicate personnel responsible for specific activities in the SoHO Entity and confirm that they are appropriately trained and competent to perform those activities, including confirmation that they have been trained in appropriate SoHO specific issues. Personnel should be retrained as necessary to remain up to date on current collection methods.

Evidence:

The auditor, as well as the applicant, will make a judgment of the adequacy of the staff support, including a review of the plan for staffing in the event of absences. The auditor should observe and inquire about the number of donors for whom one staff member is responsible at one time. The auditor may request review of dated personnel records demonstrating competency and experience. The auditor should not request or be given confidential information such as the staff's medical records (e.g., vaccinations and health records).

STANDARD:

00.034 There must be an organisational chart in which the relationships between key personnel are clearly shown in the managerial hierarchy

STANDARD:

00.035 Tasks and responsibilities must be clearly defined, understood and documented. All personnel should have clear, documented and up-to-date job descriptions. There should be an organisational chart that describes the structure of the organisation with clear delineation of responsibilities and lines of reporting.

Explanation:

There should be an organisational chart that demonstrates the structure of the organisation and the relationships and relative ranks/level of authority of its key personnel

Evidence:

All personnel should have up-to-date job descriptions, which clearly set out their tasks and responsibilities. The correct understanding of responsibilities by individuals should be assessed and recorded

STANDARD:

00.036 There is an identified person who is responsible for all activities carried out in their organisation, along with a designated person who takes over this responsibility in their absence.

Explanation:

The responsibilities of the RP should include (but are not limited to):

- ensuring that SoHO in the establishment for which that person is responsible, and intended for human applications, are donated, collected/procured, tested, processed, stored and distributed (including import and export) in accordance with EU regulations and the laws in force in the member state;
- providing information to the competent Health Authority on any substantial changes to its activities;
- implementing appropriate control measures in order to ensure compliance with the requirements of EU Regulation⁷;
- keeping records of their activities, including the types and quantities of SoHO procured/collected, tested, preserved, processed, stored and distributed, or otherwise disposed of, and on the origin and destination of the SoHO intended for human applications;
- ensuring that the competent Health Authority(ies) is (are) notified of any serious adverse reactions and events (SARE) and is (or are) provided with a report analysing the cause and the ensuing outcome;
- Ensuring that a quality system is in place and according the principles of good practice;
- providing training and qualifying personnel directly involved in activities relating to the collection / procurement, processing, preservation, storage and distribution of SoHO.

STANDARD:

00.037 SoHO establishments are required to have an identified medical specialist/physician

Explanation:

This person may or may not be the RP.

There shall be a licensed Physician with a minimum of two (2) years postgraduate certification, with training and practical and relevant experience in SoHO activities.

The physician shall be responsible for at least the following tasks (defined in the *article 49 of the EU SoHO Regulation*⁷):

(a) development, review and approval of procedures for establishing and applying SoHO donor eligibility criteria, procedures for SoHO collection and criteria for the allocation of SoHO;

(aa) supervision of the implementation of procedures referred to in point (a) when they are carried out by SoHO entities contracted by the SoHO establishment;

(b) the clinical aspects of investigation of suspected adverse reactions in SoHO donors, SoHO recipients and offspring from medically assisted reproduction from the perspective of the SoHO establishment;

(c) design and supervision, in collaboration with treating physicians, of clinical data collection activities to acquire evidence gathering to support applications for SoHO preparation authorisations pursuant to Article 41;

(d) other tasks of relevance to the health of SoHO donors, SoHO recipients and offspring from medically assisted reproduction of SoHOs collected or supplied by the SoHO establishment.

Evidence:

To fulfil this standard, the physician must provide a copy of his/her current state, provincial, or national license. Since documentation of the medical degree is required to obtain a medical license, the license will be considered to be documentation that evidence the qualifications of the physician.

This documentation is submitted with the SoHO establishment's application and should be available to the auditor prior to the on-site audit.

Example(s):

Experience can include training as part of a residency or fellowship programme, specific training in another SoHO Entity, and/or on-the-job training.

STANDARD:

00.038 The SoHO Entity must identify at least one person with responsibility for Quality Management.

Explanation:

The functions of establishing and maintaining the system to review, modify, and approve all policies and SOP intended to monitor compliance with these Standards or the performance of the SoHO Entity.

The Quality Manager figure may exist in larger entities and may not exist in smaller entities. When the individual QM does not exist, the responsibilities normally are shared with the Processing and or QC responsible

Evidence:

Auditors should evaluate if the responsibilities of the QM are correctly assigned. Definition of QM's responsibilities are detailed in the EDQM guide.

Example(s):

A Quality Manager's CV, a job description, organisational chart, audit reports, or proficiency test reports (if applicable) are all examples of documentation that may demonstrate compliance. A Quality Manager may have an operational role in the SoHO Entity as long as he/she does not audit his/her own work. In this scenario, it is acceptable for the individual's job description to state "other duties as assigned," rather than specifically list out QM responsibilities as long as there is documentation of who is assigned the role.

STANDARD:

00.039 Processing and quality control activities must be independent of each other to ensure effective and reliable evaluation of processes, and be performed by different individuals

Explanation:

it is recognised that in practice this separation of responsibilities may be difficult to accomplish in smaller SoHO Entities, where due to staffing constraints individuals may have to perform both processing and quality control activities. It is however strongly recommended that individuals do not take responsibility for quality control checking of activities that they themselves have performed

Example(s):

Per example: processing employees can contribute to quality control activities, as long as the RP and the quality department sign off on the results after checking them.

STANDARD:

00.040 Traceability must be ensured to personnel performing critical tasks, namely processing or approving critical results or documents

Explanation:

Appropriate registries should allow to trace back the critical information related with the authorised operators and evaluators (e.g. clinician responsible for donor screening and/or tissue release) involved in the different processes with impact for SoHO's quality and safety

Example(s):

If such personnel sign paper documents, whether regularly or occasionally, personnel signature lists must be available

Alternative means of registry such as journaling (digitally) associated with automated processes.

STANDARD:

00.041 Personnel must be provided with initial/basic training, updated training as required when procedures change or when scientific knowledge develops, and adequate opportunities for relevant professional development. programme

Example(s):

The training programme must ensure and document that each individual:

- has demonstrated competence in the performance of their designated tasks;
- has an adequate knowledge and understanding of the scientific/technical processes and principles relevant to their designated tasks;
- understands the organisational framework, quality system and health and safety rules of the establishment in which they work; and
- is adequately informed of the broader ethical, legal and regulatory context of their work.

STANDARD:

00.042 A suitable training programme must be in place, and be adequately resourced, and target all the personnel that might be involved in any SoHO activities

Explanation:

Training programmes should be periodically re-evaluated, and the competence of personnel must be monitored regularly.

Evidence:

This can be done, for example, by the monitoring of quality indicators, proficiency testing, external quality assurance, and internal or external audits.

STANDARD:

00.043 Standard universal precautions and appropriate procedures must be in place to avoid transmission of infections and suitable personal protective equipment (PPE) must be applied to protect personnel from these risks.

Explanation:

Documented procedures should be in place describing the actions to be taken if an individual is directly exposed to the blood or other SoHO of a donor or their donation (e.g. needle-stick injury).

Example(s):

These procedures might include accelerated and extended testing of the donor, rapid testing of the staff member, and prophylaxis for the transmissible agent(s), where appropriate. Procedures should define rules for personnel hygiene and safety and the behaviour of the personnel

Premises

STANDARD:

00.044 Premises must be designed, located, constructed, adapted and maintained to suit the operations to be undertaken

Explanation:

Their layout and design must aim to minimise the risk of errors and permit operations to proceed in an orderly sequence. Their layout must also allow effective cleaning and disinfection to avoid contamination and cross-contamination.

STANDARD:

00.045 There must be secured and controlled access to designated areas for the SoHO procedures and for storage of equipment, supplies, and reagents

Explanation:

Storage areas for SoHO must be designated and controlled to prevent mix-ups and contamination regardless of the duration of the storage.

Storage includes temporary holding of a SoHO after collection/procurement and prior to transport or shipping to a processing facility.

It is critical that the storage area be, at a minimum, secure and temperature-controlled and that the products be appropriately labelled and segregated.

STANDARD:

00.046 There must be a mechanism to monitor the flow of supplies and reagents within the SoHO organisation to prevent the use of outdated/expired supplies and reagents

Explanation:

This system should also be able to identify the location and allow the trace back of a given lot of a critical supply or reagent (that comes into contact with the SoHO), in the event that there is a manufacturing recall

STANDARD:

00.047 An effective system should be in place to ensure that expired consumables and reagents are not released and used.

Explanation:

Premises must include adequate dedicated areas that allow the 'first in, first out' – or, when applicable, the 'first expired, first out' – principle for critical consumables and reagents to be respected.

These areas should allow for adequate (physical or electronic) segregation of those materials in quarantine from those released for use.

STANDARD:

00.048 The SoHO entity must document facility cleaning and sanitation/disinfection and maintain order sufficient to achieve adequate conditions for operations

STANDARD:

00.049 All waste generated by the activities of a SoHO Entity must be disposed of in a manner that minimizes any hazard to facility personnel and to the environment in accordance with Applicable Law

Explanation:

Poor management of medical/biohazardous waste exposes personnel, waste holders, and the community to potential injuries, infections, and toxic effects. Hazardous waste generated by the SoHO Entity's activities includes a broad range of materials, including used supplies, sharps, chemicals, and the SoHO themselves. All medical/ biohazardous waste must be discarded in a safe manner according to written protocols for the disposal of biohazard waste and in accordance with Applicable Law. Contaminated materials shall be placed in appropriate bags and containers marked with the international infectious substance symbol. General waste that contains information that would constitute a breach of confidentiality if it became available to unauthorized persons, such as paper, compact discs, etc., should be stored in a secured container before disposal and ultimately shredded or destroyed.

Evidence:

Auditors should examine how medical waste and chemicals are handled and discarded (e.g., incinerator, waste field) and compare their observations with the written protocols.

Example(s):

Contaminated materials may be typically discarded after autoclaving, decontamination with hypochlorite solution, ultra-high temperature incineration, and, in some locations, through the use of a sanitary landfill. Sharps like needles, blades, etc., whether or not they are infected, should be considered highly biohazardous waste and placed for disposal in puncture proof containers. Chemicals such as cytostatic drugs, used in purging procedures, shall be discarded in accordance with applicable regulations.

STANDARD:

00.050 Personal, protective equipment (including gloves and protective clothing) must be used while handling biological specimens. Such protective equipment must not be worn outside the work area.

Explanation:

SoHO Entities must follow their institutional policy regarding appropriate personal protective equipment (e.g., gowns, goggles, plastic apron, gloves). All persons who may be exposed to blood or body fluids must utilize appropriate personal protective equipment. This includes those exposed to SoHO. The type of exposure that may be encountered will determine the appropriate suitable protection. If aerosol exposure is likely, a mask, goggles, and gowns or aprons should be worn. Gloves must be worn whenever potential infectious exposure exists. To prevent the spread of hazardous substances, personal protective equipment must be removed before leaving the workspace

Equipment and Material

STANDARD:

00.051 A list or register of critical equipment must be maintained.

Explanation:

In this context, 'critical' means those items of equipment that come in contact with the SoHO or critical consumables and reagents or influence the quality/safety attributes of the SoHO consumables and reagents either directly (e.g. a freezer) or indirectly (e.g. donor testing equipment)

Evidence:

All equipment on this list must be designed, identified, qualified, maintained and, if applicable, monitored, to suit its intended purpose and it must minimise any hazard to donors, recipients, operators or the quality and safety of the SoHO

STANDARD:

00.052 Equipment must conform to international standards and EU and national licensing arrangements, where these exist

Explanation:

In the EU, critical equipment must meet the requirements of Regulation 2017/745 of the European Parliament and of the Council of 5 April 2017 concerning medical devices and Regulation 2017/746 of the European Parliament and of the Council of 5 April 2017 on in vitro diagnostic medical devices

STANDARD:

00.053 All new critical equipment must be qualified before being put into service

Explanation:

This aims to assure proper functioning, and re-qualified periodically in service.

Example(s):

For example, temperature mapping of a freezer to identify temperature deviations that might affect the quality of stored SoHO

STANDARD:

00.054 Requalification intervals must be defined through risk assessment, taking into account reported deviations, monitoring results and the lifespan of the equipment.

Explanation:

Qualification and re-qualification policies should be established that ensure the correct performance of the equipment that impact the quality.

Evidence:

All qualification activities should be scheduled and recorded. This may include maintenance logs for equipment already in use.

STANDARD:

00.055 Critical measuring equipment must be calibrated at defined intervals to assure the accuracy of measurements.

Explanation:

The calibration intervals should be defined through risk assessment, taking into account reported deviations, monitoring results and the lifespan of the measuring device. Calibration results must be maintained and recorded.

Evidence:

Formal calibration reports should be approved and archived.

Example(s):

For example, micropipettes or temperature sensors, etc.

STANDARD:

00.056 Apparent deviations in the quality and/or performance of equipment must be investigated and registered promptly.

Explanation:

Outcomes of these investigations should be reported in a timely manner to the RP, who should consider and approve the CAPA to be implemented. Critical deviations from the design or the use of the device that could endanger the quality and/or safety of SoHO must be reported to the manufacturer and, where appropriate, must be reported to the Health Authority.

STANDARD:

00.057 Defective equipment must, where possible, be removed from production and quality control areas, or at least be clearly labelled as defective. Repair operations must not present any hazard to the quality of the SoHO and must be recorded. The requalification of repaired equipment before being returned to service could be risk-based.

STANDARD:

00.058 Equipment must be designed so that it permits effective maintenance, cleaning and if applicable disinfection. Maintenance, cleaning and if applicable disinfection must be performed regularly and recorded.

Explanation:

Preventive maintenance should be scheduled as defined by the manufacturer. The cleaning and disinfection intervals should be defined through risk assessment, taking into account reported deviations, monitoring results and the validation of the cleaning and disinfection procedure.

STANDARD:

00.059 A controlled list must be constructed of all materials, consumables and reagents that come into contact with the SoHO or that influence its quality or safety

Explanation:

Detailed specifications for critical materials, reagents and consumables must be documented and, where applicable, must meet the requirements of Regulation 2017/745 of the European Parliament and of the Council of 5 April 2017 concerning medical devices and Regulation 2017/746 of the European Parliament and of the Council of 5 April 2017 on in vitro diagnostic medical devices. Once received, supplies and reagents must be stored in a manner that preserves their function and sterility. Upon receipt of supplies, kits, and reagents, audit for suitability must be documented. For items requiring storage at a specified temperature range, the temperature of the storage area must be monitored and documented.

STANDARD:

00.061 A SOP must define a release process of the materials before use

Explanation:

Batch acceptance testing or checking of each should be carried out and documented before release for use in SoHO collection/procurement or processing.

Evidence:

Manufacturers could provide a certificate of compliance for every lot/batch of critical materials, reagents or consumables supplied.

STANDARD:

00.062 Inventory records should be kept for traceability and to prevent the use of materials, reagents or consumables after their expiry date.

Example(s):

Registries (namely expiration dates and batch id) are available and should prevent the use of expired materials, reagents or consumables.

STANDARD:

00.063 Each batch of critical materials, reagents or consumables must be traceable to the session of collection / procurement or processing of SoHO in which they were used.

STANDARD:

00.064 Apparent deviations in the quality and/or performance of critical materials, reagents or consumables must be investigated and recorded promptly.

Explanation:

Outcomes of these investigations should be reported in a timely manner to the RP, who should consider and approve the CAPA to be implemented. For relevant deviations, a notice should be sent to the manufacturer and, where appropriate, must be reported to the competent Health Authority.

Outsourced Activities Management

STANDARD:

00.065 Where steps influencing the quality or safety of SoHO (i.e. critical steps) are carried out by a third party, there must be a contract or service-level agreement in place.

Explanation:

The agreement must describe the roles and responsibilities of all parties for maintaining the quality chain and the quality requirements for the service provided. Agreements should allow for audits of contracted third parties to confirm their compliance with expectations.

SoHO Entities must establish written agreements with a third party each time an external activity takes place that influences the quality and safety of SoHO collected/procured or processed in co-operation with a third party.

Agreements should be dated, reviewed and renewed on a regular basis

Example(s):

Are example of critical steps, which require written agreements:

- a. testing laboratories (including donor, SoHO and environmental testing);
- b. Collection/procurement teams that are independent from a SoHO establishment;
- c. transport companies;
- d. suppliers of critical equipment, consumables and reagents;
- e. suppliers of services such as SoHO storage, processing or sterilisation;
- f. suppliers of IT services.

Documentation and Records

STANDARD:

00.066 Documentation must enable all recorded data relating to the quality and safety of the SoHO to be checked and traced, from the donor to the recipient and vice versa

Explanation:

For every critical activity, the materials, equipment and personnel involved must be identified and documented.

Documentation should include at least the following items:

- a. a quality manual, if required by national legislation or other applicable quality standards;
- b. policies and SOPs for all activities that influence the quality or safety of the SoHO, including the management of the quality system itself;
- c. specifications for materials, consumables and reagents;
- d. qualitative and quantitative specifications for SoHO;
- e. specifications for equipment;
- f. technical guidelines;

- g. contract and service-level agreements;
- h. job descriptions;
- i. instruction manuals;
- j. reliability of the traceability system;
- k. implementation and traceability of corrective measures;
- l. implementation of internal or external audits;
- m. implementation of a risk mapping as part of the quality management system, notably for critical activities.

STANDARD:

00.067 Procedures must be adopted to ensure that Quality Assurance procedures are correctly performed

Explanation:

Procedures must be adopted to ensure that:

- a. all documents issued as part of the quality management system are periodically reviewed, revised when necessary, dated and approved by authorised personnel prior to issue;
- b. only the current version of the document is in use, and its distribution is maintained;
- c. all personnel have access to documents needed for the execution of their tasks;
- d. invalid or obsolete documents are promptly removed from all locations;
- e. retained or archived documents are appropriately identified to prevent their inadvertent use.

STANDARD:

00.068 All documents relevant to the Quality Management System must be uniquely identified

Explanation:

Every organisation should choose their system to uniquely identify the documents associated with the Quality Management System

Evidence:

Example(s):

Ideally the documents should include:

- a. title;
- b. edition or current revision date or revision number;
- c. number of pages;
- d. owner, author and authoriser.

STANDARD:

00.069 Appropriate records must be maintained for all critical steps, including the rejection of non-conforming SoHO.

Explanation:

Records of preparation processes, storage and release for circulation (including distribution) enable the complete history of the SoHO to be traced and these records should be retained in a comprehensible and accessible form;

Procedures must be adopted to ensure that:

- records are reliable and a true representation of the results;
- records are legible and indelible;
- records meet the confidentiality requirements laid down in Article 14 of Directive 2004/23/EC and the

EDQM Guides;

- access to registers and data is restricted to persons authorised by the RP, and to the competent Health Authority for the purpose of audit and control measures;
- any alteration made to a record is dated and signed or, in the case of digital records, an audit trail of alterations is maintained;
- records contain the identification of the operators and date of completion of the activity and, where appropriate, the identification of any person who checked these activities.

Example(s):

Records should include at least the following items:

- a. records of the performance of operations critical to the safety and quality of SoHO,
- b. records of critical equipment, information systems, materials, consumables and reagents,
- c. records of complaints and deviations,
- d. records of CAPA,
- e. records of internal audits, external audits and audits,
- f. training and competency records of personnel,
- g. records of internal and external quality control,
- h. identification and analysis of risks and a risk-mitigation plan,
- i. donor records,
- j. information on the final destination of SoHO
- k. records of quality indicators

STANDARD:

00.070 Documentation must be retained according to applicable regulation and associated good practices.

Explanation:

Records must be retained for a period complying with local, national or EU requirements or regulations, as appropriate.

These requirements/criteria should be defined in the SOPs and should be made available to auditors.

Records can be stored on paper or any electronic support.

Example(s):

According EDQM Guides:

- Traceability data (that allow tracing from donor to recipient and vice versa) must be retained for a minimum of 30 years after clinical use.
- All records (including raw data) that are critical to the safety and quality of the SoHO must be kept for at least 10 years after the expiry date, clinical use or disposal.
- Quality system documentation and associated records should be retained for a minimum of 10 years.
- For other types of documentation, the retention period should be defined on the basis of the business activity that the documentation supports. These retention periods should be specified.

STANDARD:

00.071 A SoHO entity responsible for using personal data has to follow strict rules on data protection.

Explanation:

SoHO Entity should make sure the information is:

- a. used fairly, lawfully and transparently,
- b. used for specified, explicit purposes,

- c. used in a way that is adequate, relevant and limited to only what is necessary,
- d. accurate and, where necessary, kept up to date,
- e. kept for no longer than is necessary,
- f. handled in a way that ensures appropriate security, including protection against unlawful or unauthorised processing, access, loss, destruction or damage.

SoHO Entities should follow the current General Data Protection Regulation (EU GDPR) – The official Regulation (EU) 2016/679.

STANDARD:

00.072 Change control procedures must ensure that sufficient supporting data are generated to demonstrate that the revised process results in a product of the desired quality consistent with the approved specifications. The procedures must ensure the correct risk assessments, registries and training of the professionals

Explanation:

Change control should be carried out prior to the implementation of a revised/new process.

Written procedures should be in place to describe the actions to be taken if a change is proposed to any starting material, final product specification, equipment, environment (or site), method of production or testing, or any other change that may affect the quality of SoHO or the reproducibility of the process. All such changes should be requested, investigated, documented, traced and authorised. The likely impact of the change in facilities, systems and equipment on the final product should be evaluated (including a risk analysis). The need for, and the extent of, any re-validation or re-qualification should be determined.

The training programme should be re-assessed for any critical change in environment, equipment or processes. Training records (including plans and training plans) should ensure that training needs are identified, planned, delivered and documented appropriately by taking into account any changes to systems and equipment.

Some changes may require notification to, or licence amendment from, a national health authority.

STANDARD:

00.073 All complaints must be documented, carefully investigated and managed in an appropriate and timely manner.

Explanation:

The complaints procedure should take into consideration complaints from:

- a. living donors or entitled family members (next-of-kin) of deceased donors,
- b. personnel,
- c. third-party health professionals,
- d. clinical users, including those in another jurisdiction,
- e. patients.

A mechanism for categorising, tracking and trending complaints should be in place and should be readily available for audit. Categorisation of complaints should in any case lead to an assessment of whether the complaint is justified and is related to a potential deviation. If the latter is the case, then based on the potential seriousness and frequency of appearance, a root cause analysis and possible identification of corrective measures should be performed.

STANDARD:

00.074 All deviations/nonconformities, including (serious) adverse events and (serious) adverse reactions, from the required standards of quality and safety must lead to a documented investigation.

Explanation:

There should be an SOP in place that defines how the organisation manages deviations. This SOP should ensure that:

- the personnel responsible for managing and investigating deviations are designated;
- all deviations are to be categorised depending on how critical they are to the quality and safety of SoHO, and how frequently they occur;
- the medical significance of any deviation is considered and, where appropriate, the RP and/or clinician responsible for the collection/ procurement or clinical application is informed;
- the released SoHO are recalled and/or withdrawn as necessary;
- there is a clear allocation of responsibility to discontinue or resume processes;
- reporting of deviations in a non-punitive context is encouraged to help achieve improvements in practice.

STANDARD:

00.075 Serious adverse event or serious adverse reaction in a living donor or recipients, must be correctly managed and linked to the vigilance reporting system

Explanation:

There should be a process in place for taking immediate remedial actions. These actions should be clearly documented. Based on the estimation of occurrence and severity (e.g. risk matrix) of the deviation, a root cause analysis should be performed to identify the underlying cause or causes of the deviation. These should, where appropriate, lead to corrective action.

At regular specified intervals, the records of deviations should be reviewed to detect trends and initiate preventive actions.

Corrective actions must be documented, initiated and completed in a timely and effective manner.

Preventive and corrective actions should be assessed for effectiveness after implementation.

Serious adverse events and serious adverse reactions should be reported through a vigilance system.

STANDARD:

00.076 An effective written procedure must be in place for recalling and/or withdrawing a defective/non-compliant SoHO or those suspected of not meeting required quality or safety requirements.

Explanation:

An effective recall procedure must be in place in every SoHO Establishment, including a description of the responsibilities and actions to be taken in the case of a recall.

This written procedure must encompass the need to agree and document any CAPA that might be necessary, remembering that other SoHO collected/procured from the same donor might be affected. Therefore, a recall procedure could affect more recipients than initially presumed. If other SoHO (namely, organs, blood, tissues or cells) from the same donor were used, transplant teams should be promptly informed. The actions should be communicated to the end user, where appropriate.

This must include procedures for the notification of the relevant Health Authority/ies and all the facilities/institutions potentially affected by the recall.

A documented system must be in place for the handling of returned products, including criteria for their acceptance into the inventory, if applicable.

Evidence:

The existence of a centralised logbook or electronic database that maintains a two-way audit trail of SoHO received, with dates of use or disposal and identification of recipients, will greatly facilitate conducting a recall, so that appropriate actions may be taken.

Packaging and Labelling

STANDARD:

00.077 The system of identification for donors and recipients must be aligned with the packaging and labelling system of SoHO in such a way that a connection between SoHO, the source and the recipients exist at all times.

STANDARD:

00.078 Written procedures must be established and followed to ensure correct labelling. Each labelling phase for all SoHO must be documented. SoHO must be labelled during all phases of collection / procurement, processing, storage and distribution. Labelling must be clear, legible, indelible and unique. .

Explanation:

Before labelling a unit of donated or processed SoHO, the container must be inspected for evidence of impurities, defects, broken seals or contamination that could compromise the quality, integrity or safety of the product.

Labels attached to the containers should identify and describe the contents. The description should characterise the SoHO, and reflect key aspects of their maintenance and use. Standard nomenclature and standard international units of measurement must be used to describe the SoHO, and the processing they have undergone. Identification should provide information on traceability that links the SoHO to the SoHO establishment of origin and, ultimately, the donor. When SoHO are to be distributed internationally, language barriers should be considered, and information translated or coded to ensure understanding.

STANDARD:

00.079 Premises and procedures for the packaging and labelling of SoHO must be designed to prevent cross-contamination or mix-ups. Simultaneous operations must be avoided or, where unavoidable, adequate additional safeguards must be put in place.

STANDARD:

00.080 Primary packaging and labelling of SoHO must be done in an environment specified in SOPs.

STANDARD:

00.081 Containers intended to be used as primary packaging must be submitted to visual inspection before use and, if single-use containers are unavailable, the need for applying an adequate cleaning process must be assessed along with suitable sterilisation methods such as irradiation or autoclaving of materials and containers

STANDARD:

00.082 Labelling and packaging must be performed simultaneously, in a continuous process, to reduce the risk of mix-ups or cross-contamination. Where additional labels are applied to packaging, an automated verification step to ensure the correct match between container label and package label is recommended.

Explanation:

Before application to the container, printed labels must be carefully examined to ensure that the information they contain conforms to the corresponding SoHO. The results of this examination should be documented at identified critical stages. Labels must be designed to adhere firmly to the container under all anticipated storage and transport conditions. The label applied must not be removed, altered or obscured. A sufficient area of the container must remain uncovered to permit inspection of the contents, whenever possible.

For processing of batches that include large numbers of individual final units, a representative printed label should be included in the processing batch record.

STANDARD:

00.083 All key samples for testing or archiving and all related documents must be labelled in a legible, indelible and unique manner that ensures traceability to the donor and the associated donations. A record of the time and place the sample was taken must be included on the label or in accompanying documentation.

STANDARD:

00.084 Selected packaging material must be able to withstand the storage temperature (ambient temperature, refrigeration, freezing, cryopreservation) and the sterilisation procedure (if this is to be applied) that are needed to preserve the required characteristics of the SoHO and, if applicable, biological function.

STANDARD:

00.085 Primary packaging and transport containers used for SoHO must be validated for this purpose, and they must be suitable for use with human materials

Explanation:

Selection of packaging, or a combination of packaging systems, should result in a sealed environment that prevents leaks.

As a general rule, labels should be machine- printed for clarity. They should be printed with ink that does not run or otherwise become unreadable when exposed to water or other liquids. Labels must maintain integrity and remain attached to primary packages and transport containers at the storage temperatures. All printed labels for primary packaging, secondary packaging and for documentation intended to accompany the SoHO product should be stored in access-controlled areas.

STANDARD:

00.086 The suitability of packaging material, containers and labels for their intended purpose must be documented.

Explanation:

There should be written specifications and procedures for all packages and labels used for SoHO.

Example(s):

There should be written procedures describing the receipt, identification, quarantine, sampling, examination, testing and release of packaging and labelling materials, as well as the handling of such materials.

Continuity Planning

STANDARD:

00.087 The potential risks that may affect the continuity of a SoHO-E must be formally identified by considering possible scenarios of crisis

Explanation:

The identification of potential scenarios is particularly useful to predict “what can go wrong” based on prior experiences.

To identify potential hazards and vulnerabilities within their operations, SoHO-E should conduct comprehensive risk assessments.

For all risks the severity and occurrence should be weighed, and control measures should be devised.

Example(s):

Useful tools and references can be found in the EGALiTE Deliverables – Contingency Plans.

These tools include a template is proposed for the documentation of such a risk assessment, together with possible failures and a way to solve them

STANDARD:

00.088 A procedure describing the responsibilities and activities that come into action when an emergency occurs should be defined.

Explanation:

This procedure should be implemented in the quality manual and tested regularly

Example(s):

Useful tools and references can be found in the EGALiTE Deliverables – Contingency Plans.

PART A: DONOR SELECTION & DONATION PROCEDURES

Donation Centres

STANDARD:

A.001 The Donation Centre must collaborate with SoHO Establishments that meet EGALiTE Standards with respect to their interactions with the SoHO Donation Centre.

Explanation:

Stand-alone Donation Centres such as donor centres that provide donor management or collection/procurement activities must collaborate with SoHO Establishments that meet the EGALiTE Standards in order to be eligible for accreditation.

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When a SoHO preparation is centrally processed by a third party (SoHO Establishment), the Donation Centre may be responsible for securing collection/procurement of the SoHO. If these responsibilities are designated to the Donation Centre in written agreements, the following examples would require compliance with the Standards EGALiTE as applicable:

- Evaluation of the autologous or allogeneic living donor for suitability (medical fitness) to undergo the collection procedure.
- Evaluation of the allogeneic donor for donor eligibility (free of risks of transmission of infectious diseases).
- Collection/procurement of the SoHO.
- Temporary storage of the SoHO and transfer to the SoHO Establishment/Processing Facilities.

Evidence:

SoHO Establishment must be audited to ascertain that they meet the EGALiTE Standards in regard to their interactions with Donation Centres and vice versa.

If a SoHO Establishment is already EGALiTE accredited, this may satisfy the audit requirement.

If a SoHO Establishment is not EGALiTE accredited to provide these services, it must provide evidence of compliance with the EGALiTE Standards, including compliance with Applicable Law.

Example(s):

SoHO that require further processing procedures (namely preparation of ATMPs).

Single instances of collection for these other purposes must be incorporated into the facility's Quality Management (QM) Program.

STANDARD:

A.002 The donation center must ensure that they are able to avoid improper labelling, mix-ups, contamination and cross contamination during the activities of preparation and storage of reagents, materials and equipment.

Explanation:

The space used for collection/procurement and storage of SoHO should be well-defined and adequate and there should be designated space for preparation and storage of reagents, materials and equipment.

The Donation Centre should be able to prevent cross contamination, especially when the facility is also performing other procedures.

Evidence:

SOP or written documents that defines how material and SoHO are handled during donation activities. Also, floor plans could be used as evidence.

Donor Evaluation

STANDARD:

A.003 Financial and material incentives must not be used to encourage donations.

Explanation:

Financial incentives may influence the will of donors and/or their families (in case of deceased donor) or to continue donating despite potential risks for donors and patients.

This may influence the veracity of the information gathered during donors' evaluation, as financial incentives may lead donors to not disclose all the information necessary for a complete and adequate donor selection, thus compromising the quality and safety of the donated SoHO.

The aforementioned provision does not prevent payments that do not constitute a financial gain or a comparable advantage.

Voluntary unpaid donation, long promoted as the only ethical basis for donation of bodily material, should continue to have a central role in the donation process of any type of SoHO. Compensation to donors should cover only justifiable expenses and loss of income, and should not act as a direct or indirect incentive or inducement

Evidence:

Donor's consent states that no financial gain is associated with the donation.

STANDARD:

A.004 The limits of the consent used in the donation procedures are clearly established, made explicit and scrupulously respected. The confirmation of the validity of the consent and of the donor identity is performed during the donor evaluation procedures.

Explanation:

The scope of the consent needs to be explicit, although a balance needs to be struck.

A blanket, generic consent means that the person giving consent does not know or understand the implications of what they are consenting to; however, if the initial consent form is too detailed, it may be too restrictive.

The scope of the consent should cover not only the tests available today, but also tests that may be available in the future. To aid decision-making, donors should be provided with examples of the type of tests that may come online and the implications of them.

Whoever is giving consent should be told the circumstances in which they would receive feedback on any new findings. They should be prepared to receive such information, and the institution arranging the donation should be prepared to provide or arrange appropriate support when such information is communicated. Where there is no public health need for a donor to be told of such a result, they might choose to be given feedback only if the condition concerned has consequences for the donor's health and can be treated.

Evidence:

Auditor must assess the content of the informed consent(s) used for donation and the SOP associated with the procedure.

This evaluation should include the assessment of different documents if those are used for different types of donations, per example: Living allogeneic donation or family consent for deceased donation.

Example(s):

If the SoHO donated can be used for different purposes, i.e. therapeutic or research, this information should be clearly stated in the consent document.

STANDARD:

A.005 Standard Operating Procedures (SOP) for the correct Donor Evaluation must be in place to ensure the correct evaluation of donors.

Explanation:

SOPs should be known by all professionals involved in the donor evaluation's activities, be kept updated. Before collection, checking the donor's identity is an essential prerequisite. A proper investigation needs to gather as much information as possible about the donor, using medical records, interviews with medical staff who treated the donor (attending physician, general practitioner, nurse) and relevant information provided by the donor's relatives or legal representatives, family physician or other persons who have information about the donor's behavioural and medical history. The donor's medical suitability is assessed in accordance with the selection criteria, and after the evaluation of risk factors such as sexual behaviour, travel and exposure to sources of infection. A post-mortem examination may also provide useful information (when applicable). These criteria may vary, depending on the type of SoHO to be collected. Evaluation of Medical history must consider all critical criteria that ensure the safety of SoHO. Different criteria must be followed depending on SoHO and type of donor. SoHO establishments must define their acceptance and exclusion criteria based on the best practices defined by EDQM and ECDC.

Evidence:

SOP detailing the procedures for the correct evaluation of:

- i. medical history (including genetic disease, family history of disease and transfusion history);
- ii. social history (personal and behavioural information, including travel history);
- iii. physical examination;
- iv. psychological examination (living donors);
- v. tests for markers of transmissible disease

Example(s):

SOP with the clearly defined criteria & Donors' questionnaire/family interview script may evidence the compliance with the safety criteria.

Additional SOPs relate with donor examination may be needed (depending on the type of SoHO)

STANDARD:

A.006 The interviews must be performed, documented and signed by a suitably trained and competent authorised person and comply with national regulations. Interviews need to be conducted prior to donation, ensuring privacy throughout the process.

Explanation:

Interviews include the evaluation of all social risks and other information required for the correct assessment of the donor.

The donor or their family should feel at ease and be willing to openly respond to all questions.

Evidence:

Standardised questionnaires for anamnesis shall be well defined and SOP should be used for interviews to ensure that all the relevant information is obtained.

Evidence of training of the professionals authorised to perform such interviews shall also be available.

STANDARD:

A.007 The donation record, whether paper or electronic, must fully and accurately reflect the relevant information gained from reviewing these records and from discussions with medical or other personnel. These steps must be carried out by well-trained, competent staff

Explanation:

The records must be traceable and kept in the registries associated with donation.

Donor Testing

STANDARD:

A.008 Donor blood samples (or other analytes) from all donations of SoHO are subjected to biological tests mandated by national or other applicable legislation, or by a specific situation such as travel

Explanation:

Any risk factors in donors associated with high-prevalence areas for specific infections/diseases must be considered carefully. Scientific evidence for risk factors for certain diseases is provided by ECDC.

Depending on factors like individual travel history and specific current or past clinical abnormalities of the donor as well as the epidemiological situation, the decision can be made to carry out other optional tests, which can include screening for tropical infections such as malaria, trypanosomiasis, strongyloidiasis, schistosomiasis and viral infections such as West Nile virus and Zika virus.

In the case of paediatric donors, such infections must be reviewed for their impact in mother-to-child transmission.

The need to perform such assays, or others, must be examined on a case-by-case basis.

Example(s):

- Additional testing may be considered (depending on the donor's history and/or the characteristics of the SoHO donated):
- antibodies to Cytomegalovirus, Epstein–Barr virus, Coxiella burnetii and Toxoplasma gondii might be relevant for donor-recipient risk stratification;
- hepatitis E virus RNA (i.e. NAT).
- HTLV

STANDARD:

A.009 The laboratory(ies) responsible for donor testing must be accredited, designated, licensed and/or authorised by the competent authority

Explanation:

Such laboratories will have the knowledge, skills, resources and competence required for testing blood samples from SoHO donors and should use appropriate algorithms to ensure that their testing procedures have maximum sensitivity without loss of specificity.

They should also participate in relevant external quality assessment schemes (proficiency testing) and be subject to regular internal and external audits.

If additional biological assays are carried out, the laboratory used should be accredited, designated, authorised and/or licensed and should participate in an appropriate external quality-assessment programme

Evidence:

Auditors should be able to audit or observe documentation associated with laboratory's activities. Enough evidence should be made available to the compliance with the legal and technical requirements.

Example(s):

Specific accreditations and authorisations' certificates should be made available.

STANDARD:

A.010 If the tests are performed by an external laboratory a service-level agreement between this laboratory and the SoHO establishment is mandatory

Explanation:

The testing laboratory should comply with regulatory requirements and any other specific expectations of the SoHO establishment (e.g. time-sensitive availability of test results, record retention).

SoHO entities should evaluate and select a testing laboratory on the basis of its ability to generate reliable and appropriate results, and to keep relevant records.

Evidence:

Service-level agreement detailing all legal and technical requirements associated with the testing activities.

Example(s):

The service-level agreement should detail, at least:

- i. The obligation of the laboratory to notify the SoHO establishment when deviations occur is mandatory.
- ii. To ensure a consistent level of competence and performance, audits of the testing laboratory(ies) should be undertaken periodically by the SoHO establishment or by qualified external experts as part of the SoHO establishment's quality system.
- iii. Test records at the laboratory should be retained for 10 years at least and should include sample data, laboratory results

STANDARD:

A.011 The criteria for acceptance or rejection of SoHO based on the laboratory test results must be well defined and in place

Explanation:

There must be clearly defined procedures to resolve discrepant results. Appropriate confirmatory testing must take place. In the case of confirmed positive results, appropriate donor management must take place, including the provision of information to the donor/donor family and follow-up procedures, when applicable.

Evidence:

SOP detailing the decision tree for the acceptance and rejection of donors based on testing results.

STANDARD:

A.012 Personnel of Donation Centers involved in collecting, transporting (having particular regard to packaging, temperature, duration), storing or testing donor samples must be aware of specific sample requirements for which their assays have been validated, to ensure optimal assay performance.

Explanation:

If inadequate or otherwise compromised samples are provided to the laboratory and tested, the results may not be valid, and unreliable test results increase the risk of donor-related transmission of infectious pathogens.

Evidence:

SOPs should detail these technical requirements.

Example(s):

SOP related with the handling and packaging of donor samples.

STANDARD:

- A.013 The quality of the laboratory testing must be assessed regularly by participation in a formal system of proficiency testing, such as an external quality-assurance programme*

Explanation:

If testing is performed by an external laboratory this evidence should be auditable by the SoHO Establishment

Evidence:

Reports issued by the external quality-assurance programme should be evaluated during audit.

The evaluation of the results by the RP should also be object of audit.

STANDARD:

- A.014 Shipment conditions must be validated to avoid degradation of the quality of the test sample.*

Qualified transport containers and validated shipping conditions must be used when sending donor samples to a testing laboratory.

Evidence:

Validation & Qualification report(s) should be available.

STANDARD:

- A.015 All personnel involved in any stage of the testing process must be fully trained*

Evidence:

Training records and plans

STANDARD:

- A.016 In the case of a neonatal donor (i.e. age ≤ 1 month), the required tests must be carried out using a blood sample from the donor's birth mother.*

STANDARD:

- A.017 All donor samples must be identified with a permanently affixed label that contains information or references that link the sample and the laboratory test results to the donor*

Evidence:

Label sample should be available to auditors

STANDARD:

- A.018 The date and time when the sample was drawn must be accurately documented.*

Example(s):

SOPs should detail these technical requirements.

STANDARD:

- A.019 At least two donor identifiers, such as the donor's full name, date of birth, medical record number or other unique identifier, must be used. Unless a unique identification system is in place*

Evidence:

SOPs should detail these technical requirements.

STANDARD:

- A.020 The sample's label or associated documentation must also include some identification of the person who collected it and a description of the site on the donor's body the sample was*

taken from and, in the case of deceased donation, if the sample was extracted pre or post-mortem

Explanation:

If any donor blood samples were drawn before death, they can be assessed for use, but there must be assurance that the patient identifier (i.e., appropriate labelling) used for any such specimen is confirmed as coming from the donor so mix-ups do not occur (i.e. to avoid carrying out testing for critical communicable diseases on the wrong person)

Other donor- identification methods can be used, if validated, to ensure traceability.

Specimens of blood, serum or plasma from the same donor must not be mixed together for testing, whether collected at the same time or at a different time.

Example(s):

Description of the site on the donor's body (e.g. cephalic vein, femoral artery, subclavian artery, superior vena cava)

STANDARD:

A.021 Specific instructions from the test kit manufacturer must be followed

Explanation:

These can differ between tests.

Evidence:

SOPs should detail these technical requirements and the reason to deviate from the pre-defined procedure.

STANDARD:

A.022 The facility receiving any donor sample for testing must have an SOP in place to define the criteria for acceptance or rejection of the sample, based on collection, storage and transport conditions.

Explanation:

The testing facility should document acceptance or rejection of the sample and should share this sample status in a timely manner with an RP at the Donation Center and/or SoHO establishment.

Evidence:

SOP and associated registries should be available (when applicable)

STANDARD:

A.023 The mandatory serological tests for HBV, HCV, HIV and Treponema pallidum must be performed according to the requirements defined in the good practices

Explanation:

All assays must be carried out in serum and/or plasma samples of the donor according to the manufacturer's instructions.

Tests should be performed in individual samples, not pooled samples. See chapter 6.5.1. of the EDQM Guide Tissues

STANDARD:

A.024 NAT tests for HIV, HBV and HCV must be performed for every donor, in addition to serological tests

Explanation:

It is well recognised that NAT assays for HIV, HBV and HCV reduce the risk of inadvertent disease transmission due to the substantial decrease in window period when compared with routine serological tests. Because NAT assays are more sensitive, serious consideration should be given to carrying out NAT tests for HIV, HBV and HCV in addition to serological tests.

Molecular assays from deceased donors should be performed in individual samples (see current legislation of each country), not in pooled samples. Some of these NAT assays are combination tests that can detect HIV, HCV and HBV from a single blood specimen in one run (triplex assays), thus improving the feasibility of routine NAT for donor screening. (In the case of samples from living donors, the pooling could be accepted if the national requirements for the comparable NAT testing of blood donors are fulfilled.)

Transport & Shipping to SoHO Establishment

STANDARD:

A.025 SOPs for storage, transportation and shipping must be designed to protect the integrity of the SoHO and the health and safety of individuals in the immediate area.

Explanation:

SoHO may be transported and/or shipped from the Donation Centres to a SoHO Establishment within the same, adjacent, and/or remote buildings for immediate administration, processing, or storage.

There shall be a prospective agreement in place between the relevant Donation Centre and SoHO Establishment/manufacturer and/or courier, regarding transport and/or shipping conditions and the responsibilities of each facility.

Evidence:

SOPs for transportation and shipping shall be included in an SOP and shall address issues of packaging, labelling, temperature, identification, safety, SoHO integrity, and handling for any length of transport.

Auditor should assess if an agreement is in place and responsibilities are correctly assigned regarding the transport conditions.

STANDARD:

A.026 The SoHO primary container must be placed in a secondary container that is sealed to prevent leakage.

Explanation:

The SoHO shall be packaged to protect it from potential harm during transit and to prevent exposure of individuals involved in its transport or shipping from potentially infectious agents. Exposure is a risk to individuals in environments where damage to a (usually) liquid product container might occur and normally would involve unanticipated spillage or splashing (e.g., dropped product, motor vehicular accident). Primary containers shall be placed in a secondary securely sealed container such as a zip- type bag. All SoHO, regardless of infectious disease testing, shall be considered potentially infectious.

Example(s):

SOPs will vary depending on the distance, whether or not the courier and SoHO leave a building, and the nature of the outside container.

STANDARD:

A.027 The SoHO must be stored, transported or shipped to the SoHO Establishment in a validated container at a temperature defined in a SOP

Explanation:

Distribution is any transportation or shipping and delivery of the SOHO intended for human administration. It is the physical act of transferring a product within or between facilities. During shipping the product leaves the control of trained personnel at the distributing or receiving facility.

Evidence:

SOPs for transportation and shipping shall address issues of packaging, labelling, temperature, identification, safety, SoHO integrity, and handling for any length of transit.

Example(s):

For SoHO potentially contaminated during the collection/procurement procedures, refrigerated transportation is generally recommended in order to prevent the risk of bacterial proliferation.

STANDARD:

A.028 SoHOs that are transported or shipped from the Donation Centre to the SoHO Establishment must be in an outer container made of material adequate to withstand leakage of contents, impact shocks, pressure changes, temperature changes, puncture, and other conditions incident to ordinary handling.

Explanation:

SoHO temperature during transit is dependent upon a number of variables, including the transit time, ambient temperature ranges, initial temperature, size of the product, and characteristics of the specific container system. There shall be a prospective agreement among the collecting, processing, and receiving facilities, and/or the courier regarding transport or shipping conditions. Transport between facilities shall always consist of the use of an outer container that protects the product from adverse conditions encountered during transport (e.g., air pressure and temperature changes, rough handling), and has been validated to maintain the agreed upon transport temperature.

For situations where transport from the Donation Centre to the Processing Facility requires only minutes, as long as the product is transported safely, a controlled temperature environment is optional.

Transport over longer distances, for more extended periods of time, or transport outside of a building may require that a controlled temperature environment be maintained using a shipping container and method validated for the temperature range specified.

For non-cryopreserved SoHOs requiring a controlled temperature, a validated thermally insulated container should be used with cold packs added as necessary to maintain the required temperature.

Containers for transport of SoHOs that are shipped from the Donation Centre or are transported on public roads shall be made of durable material and insulation that will withstand leakage of contents, shocks, pressure changes, and temperature extremes. The containers shall be validated prior to use to achieve proper performance for all expected extremes and maintenance of desired internal temperature.

Re-validations should be considered whenever the conditions of the original validation have changed (i.e. different ranges of temperature, packaging conditions)

Evidence:

Validation plan and rationale to define the periodicity of re-validation

PART A.1: LIVING DONATION

This section of the standards pertains to the SoHO entities responsible for the donation of SoHO obtained from living donors, whether collected as surgical residues (e.g., umbilical cord blood and placenta following childbirth, femoral heads removed during hip joint replacement surgery, heart valves from patients undergoing heart transplant) or otherwise. It encompasses activities related to the recruitment of living donors (including related donors), with the aim of informing individuals about SoHO donation activities or encouraging them to donate SoHO.

Evaluation of Living Donors

STANDARD:

A1.001 Procedures for recruiting living donors in an ethical manner, for ensuring their safety and well-being and for the identification and referral of all potential deceased donors must be implemented and maintained in accordance with the applicable legislation.

STANDARD:

A1.002 Professionals involved in the recruitment of living donors, and in the identification and referral of deceased donors, must be trained and appropriately qualified

STANDARD:

A1.003 All living donors must receive complete information before giving their consent. This information must be provided by a trained professional. Moreover, it must be impartial and, whenever possible, given by a treating physician who is not treating the recipient of the SoHO

Explanation:

This is intended to prevent any conflicts of interest.

STANDARD:

A1.004 The donation of SoHO by living donors must take place in an environment that ensures their health, safety and privacy. There must be suitable space for confidential examination and evaluation of living donors.

Evidence:

The auditor will observe the Donation Centre to determine if the collection environment is adequate to minimize the risk of introduction, transmission, or spread of communicable disease.

STANDARD:

A1.005 Suitable premises must be available for confidential interviewing of living donors.

STANDARD:

A1.006 In case there are absolute contraindications for autologous donors, they must be clearly documented

Explanation:

The potential benefits and risks should be analysed on an individual basis and a decision made by the clinician in charge, subject to full informed consent from the patient. This process should be clearly documented

Evidence:

Audit should assess the contraindications defined for each type of SoHO.

No evidence needed if no absolute contraindications apply.

Example(s):

Contraindications shall be clearly defined in the SOPs.

STANDARD:

A1.007 The information on medical and social history required for donor evaluation must be obtained directly from the donor

Explanation:

Additional information, where applicable, should be sought from other sources, similar to that obtained for deceased donors. The types and extent of records to be reviewed will vary depending on the type of donation.

STANDARD:

A1.008 If collection / procurement from a living donor involves a directed donation, the recipient's identification must be documented to ensure traceability

Living Donor Testing

STANDARD:

A1.009 Blood sampling must be obtained at the time of donation or, if this is not possible, within 7 days before or 7 days after donation. (Note: this standard is not applicable for blood donation activities)

Explanation:

If SoHO of allogeneic living donors can be stored for long periods before use, repeat sampling and testing is required after 180 days, unless specific exemption criteria are met

STANDARD:

A1.010 The risk of transmission of infection to personnel, during collection, processing and storage of SoHO, must also be considered

Evidence:

Written standard operating procedures (SOPs) should be present for these situations

PART A.2: DECEASED DONATION

Evaluation of Deceased Donors

STANDARD:

A2.001 Physicians determining the death of a potential donor are not directly involved in SoHO collection from the donor or subsequent transplantation /transfusion procedures and are not responsible for the care of any intended recipient of such SoHO.

STANDARD:

A2.002 SoHO must not be removed from the body of a deceased person unless that person has been certified dead in accordance with the national law and consent or authorisation has been obtained.

STANDARD:

A2.003 Suitable environment and/or premises must be available for confidential interviewing of the families or friends of deceased donors.

Explanation:

Right conditions to perform family interviews should be ensured either for face to face or telephonic interviews.

Donation centers should document and provide evidence on how they perform such procedures.

Evidence:

Auditors may review the SOPs pertaining to interviews with the donor's family.

Deceased Donor Testing

STANDARD:

A2.004 Assays must be specifically validated for use for the sample type (e.g. plasma, blood, urine, seminal fluid, respiratory swabs, etc.)

STANDARD:

A2.005 Blood samples must be obtained just before cardio circulatory arrest or, if this was not possible, the time of sampling must be as soon as possible after death, and in any case within 24 h after death.

Explanation:

It is important to collect blood samples without untoward delay after death to avoid sample characteristics that could cause a non-specific test result (e.g. partial haemolysis) or that could lead to its rejection for testing (e.g. complete haemolysis). Delays in donor sampling have been shown to increase the incidence of red cell haemolysis, and other substances can appear in non-circulating blood due to growth of micro-organisms and release of enzymes (including by-products of tissue and cell death)

STANDARD:

A2.006 All infectious disease testing kits used to analyse these samples from deceased donor must be validated for use of samples collected after death (and under different circumstances)

STANDARD:

A2.007 Where haemodilution is known to have occurred, ideally pre-transfusion/ infusion samples must be obtained for testing purposes

STANDARD:

A2.008 Assessment of the extent of any haemodilution includes the use of a formula to calculate dilution of the donor's original circulating blood volume (and circulating levels of antigen and/or antibody, if present) and must be done by the physician in charge or the transplant coordinator.

Evidence:

Current practice is to consider 50 % calculated haemodilution to be the maximum allowable with minimal risk of a false-negative test result arising because of the haemodilution.

Further possibilities for calculating haemodilution have been developed taking into account different physiological conditions. These calculations should only be used after extensive studies and in compliance with the specifications of the algorithm suggested in the EDQM Guide

PART B: COLLECTION

STANDARD:

- B.001 The SoHO Entities must have written agreements with each person (if freelance), clinical team or third-party organisation involved in carrying out collection/procurement, as well as those collecting critical information used in donor selection.*

Explanation:

This aims to promote compliance with donor-selection criteria and procurement procedures.

The written agreements must include detailed descriptions of expectations and responsibilities related to quality and safety measures, as well as any additional regulatory requirements. A written agreement is not necessary for individuals directly employed by the same TE or organisation responsible for these steps but expectations and responsibilities pertaining to procurement must appear in their job description

STANDARD:

- B.002 Facilities in which SoHO are collected must meet appropriate grades of air quality and cleanliness. The collection sites must be fit for purpose and a risk assessment must be carried out to determine the suitability of the collection procedure*

Explanation:

The appropriate standard of cleanliness will depend on the type of SoHO being collected/procured, the degree of exposure of the SoHO during the collection/procurement process, and the decontamination or sterilization processes that will subsequently be applied during processing.

The suitable grade of air quality and cleanliness may be determined by an adequate risk assessment, considering all the processes associated with SoHO collection and processing. MiRCA tool may assist professionals in this assessment.

STANDARD:

- B.003 Access to the area where collection takes place must be restricted to essential personnel during the actual recovery of SoHO*

STANDARD:

- B.004 The room where collection/procurement takes place must meet the following requirements:*
- a. adequate floor area, and ancillary work areas (e.g. work-tops and benches);*
 - b. appropriately located and access controlled to ensure privacy;*
 - c. furnished with sufficient and suitable lighting;*
 - d. in a good state of maintenance;*
 - e. able to provide a sufficiently clean and cleanable environment that will not increase the risk of contamination of the SoHO;*
 - f. comfortable in temperature and humidity for living donors and procuring staff.*

STANDARD:

- B.006 There are procedures in place to minimise the risk of contamination must include the cleaning of working surfaces with an appropriate and effective disinfectant.*

STANDARD:

- B.007 Collection of SoHO must follow aseptic procedures.*

Explanation:

The collection area should also be cleaned and disinfected after recovery. Appropriate and safe disposal of single-use instruments, consumables and any other waste, including clinical waste that poses a biohazard, must be carried out. Any re-usable instruments must be cleaned immediately or as soon as possible following use, and sterilised before being used again

STANDARD:

B.008 If a Donation Center / SoHO Entity (or third party carrying out the collection/recovery) uses the general services of the host facility to clean the collection/procurement area and/or sterilise any re-usable instruments, the SoHO Entity must have a written agreement with the host facility, and the procedures in place must be validated and inspected.

Evidence:

Written Agreement and SOPs detailing the obligation to comply with the technical requirements and communication of any event related to the facilities.

Example(s):

Communication of any contamination detected in the collection facilities

Equipment and Materials

STANDARD:

B.009 Materials and equipment used during collection must comply with the relevant national and international regulations, standards and guidelines for the intended use of the donated SoHO

Explanation:

All equipment and materials that may have direct contact with SoHO should be sterile, single use (where possible) and CE-marked for their intended purpose (where available).

Example(s):

Materials (i.e. consumables and reagents) and equipment (i.e. surgical instruments, packaging and containers)

STANDARD:

B.010 Instruments or devices must be suitable for their intended use and must be maintained in good working order.

Explanation:

Requirements must be described in the SOPs and include its visual inspection and scheduled calibration of measurement devices, where appropriate, against relevant defined standards at specified intervals.

STANDARD:

B.011 When re-usable instruments are used, a validated cleaning, disinfection, packaging and sterilisation process for removal of infectious agents must be used and documented.

Evidence:

SOPs and associated forms/registries should be evaluated during inspection.

STANDARD:

B.012 A traceability and tracking system must be in place for operators and critical equipment/materials, for each SoHo collection event, and for the donor.

STANDARD:

B.013 Personnel conducting collection/procurement activities must be provided with protective clothing appropriate for the type of collection.

Example(s):

Usually, to retrieve tissues, this will involve wearing a sterile gown, sterile gloves, glasses and a face shield or protective mask.

STANDARD:

B.014 When applicable (i.e. tissue procurement), approved materials necessary for reconstruction of a deceased donor's body must be provided.

Identification, packaging, containers and labelling

STANDARD:

B.015 At the time of procurement, SoHO must be uniquely identified

Explanation:

A unique identification number or code must be allocated to the donation and to donated SoHO during collection/procurement, or at the end of the recovery process, to ensure appropriate identification of the donor and traceability of all donated material.

STANDARD:

B.016 The labels must be appropriate to ensure identification and traceability of SoHO and must be designed to adhere firmly to the container.

Explanation:

When SoHO are shipped from the procurement site to the SoHO establishment, the transport container must correctly labelled

Labels must be resistant to storage conditions to avoid the loss of identification of SoHO.

STANDARD:

B.017 If secondary packaging is used after collection, it must comply with the same requirements as those established for primary packaging.

Explanation:

If labels with all the required information are not attached to the primary packaging they should be attached to the secondary packaging, which should be closed and sealed, ensuring that any unique identification number on the primary label is present on the label for the secondary pack and on accompanying documentation.

Evidence:

Observation of sample labels and associated SOPs to determine its correctness

STANDARD:

B.018 SoHO collected for research purposes must be clearly identified as such on their packages and labels (e.g. 'FOR RESEARCH USE ONLY' or 'NOT FOR CLINICAL USE').

Collection Procedures

STANDARD:

B.019 Written SOPs for collection must be in place, based on the requirements of the relevant Health Authority, the EDQM Guide and the expectations of the SoHO Establishment or end-user needs. (Detailed criteria are outlined within the specific chapters dedicated to SoHO in the EGALiTE Standards)

Explanation:

These SOPs must outline the correct steps to be taken for each stage of SoHO collection. Procedures that ensure contamination control must be applied, including use of aseptic techniques, sterile materials and equipment and appropriate clothing for the personnel conducting the procurement. Procurement SOPs must be reviewed by an authorised person periodically (or as required) and updated as necessary.

Procedures must be authorised and appropriate for the type of donor and the type of SoHO procured, and must be validated

These steps must include the following requirements:

- a. verification of the donor's identity and what constitutes evidence of donor (or the donor family's) consent or authorisation;
- b. where necessary, ensure that permission from any relevant legal authorities (for example, judges or coroners) has been obtained before SoHO are collected/procured;
- c. assignment and appropriate use of a unique identifier/code;
- d. knowledge of selection (risk) criteria required for donor assessment, including physical examination of the donor and mandatory infectious disease testing required;
- e. knowledge of the types of blood and other samples required for mandatory laboratory tests to ensure that they are of appropriate quality;
- f. steps that minimise the risk of microbiological contamination during collection;
- g. collection steps that protect the properties of the SoHO required for clinical use;
- h. for deceased donation, how to reconstruct the donor's body so it is as similar as possible to its original anatomical appearance;
- i. confirms if the warm ischaemia time is within the defined ranges.
- j. considerations for packaging, labelling and transportation of collected SoHO to the SoHO Establishment or, in the case of direct distribution, to the clinical team responsible for their human application or direct use;
- k. considerations for collecting, packaging, labelling and transporting samples of donor blood or other samples to the laboratory for testing;
- l. procedures that protect the health and safety of the living donor;
- m. how to register deviations from the approved procurement procedure.

STANDARD:

B.020 To minimise the risk of SoHO contamination by collection personnel who may be infected with a transmissible disease, policies and procedures must be established and followed to address this risk

STANDARD:

B.021 Procedures and policies that minimise the risk of microbiological contamination during collection/procurement must be considered

Explanation:

These include:

- a. the personnel allowed to be present during collection/procurement should be defined and such restrictions respected;
- b. preparation of the donor's collection site must follow the recommended standards of practice used for surgical patients and must occur at the beginning of procurement using an appropriate antimicrobial agent designed for this purpose;
- c. the procedure for the disinfection of the recovery site should account for the reduction or elimination of bacterial spores as well as vegetative micro-organisms, and should include the type of suitable disinfectants, their concentrations and durations of exposure. This procedure may be defined by the hospital when the collection of SoHO takes places within the normal activities of an operating theatre;
- d. before use, all materials and equipment must be visually inspected by collection personnel to ensure that they meet specifications (e.g. sterile, seals not broken, equipment functioning as expected, expiration date);
- e. for deceased donation, it is advisable to collect SoHO before the autopsy takes place but, if this is not possible, detailed procedures must be written to address the increased potential for contamination when collection takes place after autopsy.

Example(s):

SoHO establishments could define procedures to collect SoHO up to 72 h after cardiocirculatory arrest, if this has been validated.

STANDARD:

B.022 Collection must include procedures that protect those properties of SoHO required for their ultimate clinical use

Explanation:

These procedures generally include:

- a. post-mortem time limits – it is recommended that tissue should be recovered within 24 h after cardiocirculatory arrest, provided that the body has been cooled or refrigerated within 6 h of cardiocirculatory arrest (to reduce the risk of tissue degeneration and microbiological growth). If the body was not cooled or refrigerated within 6 h of cardiocirculatory arrest, tissue should be recovered within 12 h of cardiocirculatory arrest. Alternative time limits should be validated by quality assessments and tests for microbiological contamination. It may be possible to extend the post mortem interval up to 48 h or 72 h after death if processing has been validated to guarantee quality and microbiological safety (in which case the blood samples for serological testing must be still taken within 24 h after death, as specified in EU SoHO Regulation and/or EDQM Guides, to minimise the risk of blood deterioration);
- b. preservation of important anatomical structures and other SoHO characteristics;
- c. temperature requirements during storage and transport to the next destination;
- d. avoidance of delays in transport due to time limits in place for processing after collection/procurement.

STANDARD:

B.023 The roles of the individual team members for SoHO collection, must be defined by SOPs.

Example(s):

In every deceased-donor procurement team, an appropriately trained senior person must take overall responsibility to ensure that SOPs are adhered to and that the following tasks are carried out to the required standards:

- a. identification of the donor;
- b. review of donor documentation, including medical history, laboratory tests (if completed), lawful consent/authorisation;
- c. physical examination of the donor;
- d. organisation and co-ordination of the procurement;
- e. evaluation of abnormal procurement findings;
- f. review of tissue packaging and labelling;
- g. review of donor reconstruction;
- h. completion of all required procurement documentation.

STANDARD:

B.024 For the deceased donations, the collection/procurement report must contain:

- a. a sufficiently detailed summary of the events surrounding death;*
- b. the date and time of donor death and SoHO collection/procurement (and, where relevant, start and end times) to facilitate determination of the time interval from death or cross clamp to collection/procurement;*
- c. the date and time of, and quantity of, blood collection for donor testing (when applicable);*
- d. the conditions under which the donor body was kept before collection/procurement (whether or not the donor body was cooled or refrigerated and, where appropriate, the time when cooling or refrigeration began and ceased);*
- e. if possible, whether collection/procurement took place before or after autopsy and whether or not an autopsy is planned;*
- f. when applicable, a description of other SoHO from the same donor sent to different SoHO Establishments, including their identification;*
- g. if applicable, information regarding reconstruction of the donor's body.*

STANDARD:

B.025 If processing (excluding close systems), including decontamination, shaping, cleaning, sizing and final packaging (for direct distribution) at the collection site is unavoidable, the collection area must fulfil the criteria of a processing area

Explanation:

Processing duration and extent must be limited to the minimum, and a Grade A air-quality environment (surrounded by, at least, Grade D air quality) is required for the open processing steps.

Procedures (such as washing steps and incubation in antibiotics) which do not involve processing, might be considered part of the collection procedure.

Evidence:

Records supporting the qualification and monitoring of the processing site must be available for inspection. Selection of the use of suboptimal conditions must be supported by written justification and be authorised by the relevant Health Authority

STANDARD:

B.206 SoHo Establishments must have procedures in place that address the retention of collection records, which must include descriptive documentation of the steps taken, the materials and equipment used, and identification of the personnel involved

Explanation:

Collection/Procurement records must be sufficiently detailed to facilitate robust and reliable traceability, to provide a complete history of the work undertaken and to be capable of linking the records to the particular donor of the collected SoHO

Evidence:

Such records must be clear and legible, protected from unauthorised amendments, retained and readily retrievable throughout a specified retention period, and must comply with data- protection legislation.

STANDARD:

B.027 A unique identifier (e.g. a donation number for a donation event and/or a donor identification number) must be allocated to the donor as well as the collected/ procured SoHO

Explanation:

This coding must be in place to ensure an effective and accurate system capable of tracking tissues throughout all stages, including an identifiable link to the procurement steps.

STANDARD:

B.028 To ensure that all steps are traceable and verifiable, the SoHO Establishment (or Donation Centre) must produce a report, recorded at the time of collection/procurement, which must be forwarded in time to the location where processing takes place.

Evidence:

SOP and/or report(s) being available

Example(s):

This report, depending on the type of donor, could contain the following:

- a. donor identification data (donor code, donor given name, family name, date of birth and sex, as well as how and by whom the donor was identified) or donor identification.
- b. unique coding number, which will be either the donation identification sequence of the Single European Code (SEC) for EU countries, or a code generated by a Health Authority or by use of an internationally recognised coding system such as 128 Eurocode, or the WMDA GRID code for unrelated HPC donors (Chapter 15);
- c. the environmental conditions of the collection/procurement facility, i.e. location or description of the physical area where collection/procurement took place;
- d. a list of observations made during the physical examination of the donor's body – but, for a living donor, only when such an examination is justified;
- e. a description and identification of collected/procured SoHO, including samples for testing of infectious diseases;
- f. the identification of the person who has overall responsibility for the collection/procurement session (including his/her signature);
- g. date, time (where relevant, start and end times) and location of procurement;
- h. the type, volume, manufacturer and lot/batch/serial number of reagents, additives and the transport solution(s) used;
- i. name and address of the SoHO Establishment;
- j. name and destination of the SoHO

**STANDARD:**

B.029 For each donor, there must be a record containing the donor's identity with at least two forms of identifiable information. These coded data must be entered in a registry maintained for this purpose.

Example(s):

(e.g. given name, family name, date of birth, sex. If a mother and child (both living) are involved in the donation, records must indicate not only the name and date of birth of the mother, but also the name (if determined) and date of birth of the child)

PART C. PROCESSING, STORAGE AND RELEASE OF SoHO

Receipt at the SoHO establishment

STANDARD:

- C.001 SoHO Establishments must have a documented policy and specifications against which each consignment of SoHO (including blood samples from donors) is verified.*

Explanation:

Verification is the confirmation through the provision of objective evidence that specified requirements have been fulfilled. These specifications must include the technical requirements and other criteria considered by the SoHO Establishment to be essential for the maintenance of acceptable quality. When the collected/procured SoHO arrive at the SoHO Establishment, there must be documented verification of the consignment. Documents must be completed covering the transport – including the transport conditions, packaging, labelling and associated documentation – and samples (including blood) to ensure that they meet the requirements and specifications of the receiving establishment (and, in EU countries, the requirements of Annex IV of Commission Directive 2006/17/EC).

The packaging, the SoHO received, and any accompanying samples must all be examined to ensure that they have not been damaged or tampered with during transit.

STANDARD:

- C.002 SoHO Establishment must ensure that SoHO received are quarantined and stored in a defined, separated and adequate location under appropriate conditions until they, along with the associated documentation, have been inspected or otherwise verified as conforming to requirements.*

STANDARD:

- C.003 The acceptance or rejection of received SoHO must be documented.*

Explanation:

The review of the relevant donor/procurement information, and thus acceptance of the donation, needs to be carried out by specified/authorised persons.

Evidence:

SOPs and forms used for the acceptance or rejection of received SoHO should be evaluated.

STANDARD:

- C.004 The SoHO Establishment must have documented procedures for the management and segregation of non-conforming SoHO, or those with incomplete test results for infectious diseases, to ensure that there is no risk of contamination of other SoHO being processed, preserved or stored.*

Explanation:

SoHO must be held in 'quarantine' all the requirements relating to donor testing have been completed.

STANDARD:

- C.005 When SoHO are not being transported by SoHO Establishment's personnel, there must be agreement signed by third parties that defines the responsibilities of each party in the transport of SoHO to the SoHO Establishment.*

Explanation:

Such transport must ensure the safety of the SoHO and maintenance of their temperature conditions and prevent unauthorised access.

STANDARD:

C.006 Quality-control checks of collection/procurement and transportation methods must be reviewed regularly by SoHO Establishment s to ensure that the integrity of SoHO and the storage temperatures are maintained during collection/procurement and transit.

STANDARD:

C.007 Documented measures must be taken by the SoHO entity that receives SoHO from another country or distribute SoHO to another country to ensure that the donor-testing requirements of the destination country are met.

Evidence:

This should include the evidence of donor test evaluation criteria, performed by the RP, and evidence that any laboratory involved in testing of donor samples has been accredited, designated, licensed and/or authorised by the appropriate authority to carry out such testing.

Donor Testing and results' reporting

STANDARD:

C.008 Reporting methods must be used that link the donor's unique identifier to the samples and test results, while also keeping the donor anonymous to third parties.

Explanation:

Data-security measures are required, as well as safeguards against any unauthorised additions, deletions or modifications to donor test results.

There must be no disclosure of infectious-disease test results to unauthorised persons

Example(s):

The procedures associated with test results reporting must ensure that accurate, rapid and verifiable results are provided. In addition, there must be a system in place to ensure prompt alerts using an immediate notification system when an indicative test result for an infectious disease occurs.

Other precautionary measures in reporting may include the following:

- a. where manual systems are still used (although they are not recommended), analysis reports should be cross-checked to ensure that the transcription of test results has been confirmed by two independent assessors (the 'four eyes principle');
- b. using computerised procedures for the transfer of test results from laboratory equipment to the laboratory data-processing management system (e.g. medical records) to eliminate the need for manual transcription of data or oral information;
- c. using clearly interpretable, computerised graphic symbols to highlight pathologic results;
- d. recording (semi)quantitative values (e.g. titre, IU/mL) of antibodies and/or the related positivity threshold next to the viral negative/positive result;
- e. recording the number of copies/mL, if applicable (or, preferably, IU/mL) of nucleic acid measurement as well as (for qPCR systems) the linear range of the assay (if qualitative PCRs are used, then semi quantitative values should be recorded, e.g. Ct-Values, Cp-Values);
- f. using formal laboratory reporting structures and accreditation or certification pathways to improve quality standards;
- g. using widely recognised international units of measurement;

- h. Making available the name of the kit on demand and the data of the diagnostic assays.

STANDARD:

- C.009 Arrangements between the testing laboratory and the SoHO establishment, must include agreed methods for the reporting of test results to ensure that mix-ups are avoided and to prevent misinformation.*

STANDARD:

- C.010 Laboratories and SoHO establishments must have policies relating to the management of test results from a donor that may be pertinent to family members and other contacts of the donor or that have implications for them and public health.*

STANDARD:

- C.011 If there are no national requirements, a risk-analysis-based decision based on the type of SoHO and the type of donor (autologous, allogeneic, living, deceased, multi-organ) must be performed to decide if, and for how long, archived samples must be retained.
A storage time of at least 1 year after the distribution of the last SoHO from the donor is recommended.
In some countries, archiving donor samples may be required.*

STANDARD:

- C.012 A documented risk assessment approved by the RP must determine the fate of all stored SoHO following the introduction of any new donor selection or testing criterion, or any significantly modified processing step, that enhances safety or quality.*

Explanation:

The RP who will interpret test results must be knowledgeable about the accuracy of the infectious-disease test and the interpretation of the test results, and decisions must meet the expectations in regulations or, if regulations are not prescriptive, follow professional standards of practice or the ECDC SoHO risk assessments when they are available.

Evidence:

SOP describing the risk assessment and examples of documented assessments should be evaluated by the auditor.

RP's CV and registries of trainings can also be considered to attest the maintenance of the competence.

Processing Facilities

STANDARD:

- C.013 Processing facilities must be dedicated to this activity and must be designed, qualified and monitored to ensure that air quality is appropriate for the process being carried out.*

Explanation:

They must be spacious enough to facilitate the work and provide good ventilation.

International standards, such as the EU Guidelines to good manufacturing practices for medicinal products for human and veterinary use (known as GMP) and the ISO 14644 guidelines for Cleanrooms and associated controlled environments, provide information to help achieve the appropriate air quality.

STANDARD:

- C.014 Processing of SoHO must be carried out in appropriate cleanrooms.*

Explanation:

In these cleanrooms, the concentration of airborne particles (viable and non-viable) must be controlled to specified levels. Base in the risk analysis, an appropriate level of environmental monitoring should be defined. Whichever classification is applied, the premises and their facilities should have:

- a. floors, walls and ceilings of a non-porous material with smooth surfaces to minimise the shedding or accumulation of viable and non-viable particles and to permit the repeated application of cleaning agents and disinfectants;
- b. temperature control and (based on risk assessment) humidity control;
- c. a filtered air supply that maintains a pressure differential and airflow to adjacent cleanrooms of different cleanliness levels to prevent reversal of airflow direction between the segregated cleanrooms; a combination of negative and positive pressure can also be used to achieve specific biosafety requirements;
- d. a documented system for manual or continuous monitoring of temperature, humidity, air supply conditions, pressure differentials, and viable and non-viable particle numbers
- e. a documented system for cleaning and disinfecting cleanrooms and equipment;
- f. a documented system for gowning and laundry;
- g. adequate space for personnel to carry out their operations;
- h. adequate space for storage of sterile garments (if applicable);
- i. access limited to authorised personnel.

STANDARD:

C.015 Facilities for aseptic and clean, non-sterile processing must be dedicated to this activity, and must be designed, qualified and monitored to ensure that the air quality is appropriate for the process being carried out

STANDARD:

C.016 The environmental temperature and relative humidity must be set to guarantee the safety and quality of the SoHO, staff comfort, electrostatic charging and discharge

STANDARD:

C.017 To minimise the risk of contamination, a positive pressure must be created relative to adjacent cleanrooms of a lower grade

Explanation:

The pressure differential between adjacent cleanrooms of different grades should be at least 10 Pa (guidance values in GMP, Annex 1) with the maximal air pressure in the background environment for the Grade A zone. This forms a 'pressure cascade' to prevent reversal of airflow direction between the segregated cleanrooms and limits the entry of contamination into the cleanrooms of a higher cleanliness level.

STANDARD:

C.018 SoHO establishments must process SoHO in the equivalent of Grade A with a surrounding environment of at least Grade D (GMP classification).

Explanation:

A less stringent processing environment may be acceptable based on the results of risk analysis.

Some national requirements are more stringent, requiring Grade A with a surrounding environment B or C for certain processes. If GMP conditions are required, aseptic processing must be done in a Grade A zone within a Grade B background environment.

Example(s):

The specification of the air quality of the processing environment should be decided on the basis of the particular types of SoHO and the processing method that is being applied. Based on a risk assessment, several factors (such as limitations of sampling methods, contamination during manipulation, use of antimicrobials, transfer of contaminants at transplantation) should be taken into consideration when determining the air-quality specifications, especially when less stringent conditions are applied. Where the risk of SoHO contamination during processing is high, and the chances of any contaminants being transferred to the recipient are high, a more stringent air-quality specification should be adopted.

EDQM MirCA Tool can be used to produce evidence of the risk assessment. A less stringent processing environment could be considered if one of the following applies:

- a. a validated microbial inactivation or validated terminal sterilisation process is applied; or,
- b. if it is demonstrated that exposure in a Grade A environment has a detrimental effect on the required properties of the SoHO concerned; or,
- c. if it is demonstrated that the mode and route of application of the SoHO to the recipient implies a significantly lower risk of transmitting bacterial or fungal infection to the recipient than with transplantation of SoHO; or,
- d. if it is not technically possible to carry out the required process in a Grade A environment (e.g. due to the requirements for specific equipment in the processing area that is not fully compatible with Grade A (Directive 2006/86/EC)).

STANDARD:

C.019 Processing environments must be qualified and monitored in accordance with EN ISO 14644, EN 17141 and EU GMP Annex 1.

Explanation:

Qualification of cleanrooms and clean zones is required to support and verify the operating parameters and the limits for critical parameters.

The specified acceptance criteria set should be verified, and therefore testing of certain parameters and specifications should be performed.

The validation master plan should be built following a risk-assessment exercise aiming to define the extent and frequency of the qualification tests in a proportional manner to the risks identified. The validation plan should consider the initial and consequent qualification, as well as the at-rest and in-operation classification. The qualification strategy should consider the monitoring strategy displayed over the process.

Whenever a particular process is submitted to a continuous air-quality monitoring programme, the frequency of qualification of cleanrooms, laminar airflow workstations, isolators and restricted access barrier systems (RABS) might be adapted accordingly to a less stringent programme.

STANDARD:

C.020 Processing and storage facilities must be cleaned, and if applicable disinfected, according to a schedule and procedure that has been validated to achieve the required level of cleanliness, and all cleaning and disinfection procedures must be documented

Explanation:

Sanitation and disinfection procedures must be well defined in an SOP and registered

Processing Activities

STANDARD:

- C.021 Processing of SoHO must be carried out within a comprehensive quality-management system, must be documented using SOPs and must be thoroughly validated, to demonstrate that the quality and efficacy of the final product have not been unacceptably compromised and that contamination or cross-contamination has not been introduced during processing*

STANDARD:

- C.022 If a SoHO Establishment entrusts one of the stages of processing to a third party, a written agreement is needed between the SoHO Establishment and the third party.*

Explanation:

The SoHO Establishment must evaluate and select third parties on the basis of their ability to meet the established standards.

STANDARD:

- C.023 Maximum times from collection/procurement (or circulatory arrest) until processing and storage must be defined. Procurement, processing and storage times must be documented in the records for SoHO.*

STANDARD:

- C.024 In order to avoid cross-contamination, the SoHO from one donor must not come into contact, at any time during processing or storage, with SoHO from another donor (unless they are intentionally pooled (i.e. Platelets))*

STANDARD:

- C.025 A separate set of clean, sterile instruments must be used for each donor.*

Explanation:

Where possible, these should be single-use and disposable. In some cases, e.g. for ocular tissue, single-use surgical instruments for procurement and processing are available and recommended. Each SoHO product should have a batch number that is also recorded in the processing records.

STANDARD:

- C.026 SoHO establishments must have a monitoring plan that specifies:*
- a. acceptance limits of microbial contamination (action level, alert level);*
 - b. sampling plan and frequency;*
 - c. sampling methods and equipment;*
 - d. sampling culture media and incubation of samples;*
 - e. analyses and evaluation of results (including trend analyses);*
 - f. handling of out-of-specification results.*

Explanation:

To define and control microbiological hazards it is necessary to identify the potential risks relating to each processing step and the potential risks of the SoHO themselves, as well as the probability of these risks and the mitigation actions intended to minimise the risks.

Selection of the microbial monitoring method should involve consideration of the risks generated by sampling during processing. The sample sizes taken for monitoring purposes will usually be a function of the sampling rate of the system used. It is not necessary for the sample volume to be the same as that used for formal qualification of cleanrooms and clean-air devices. Microbial samples can be taken using four sampling

methods: volumetric air sampling, settle plates, contact plates and glove prints – or fingerprints. A non-selective culture medium, permitting growth of the expected micro-organisms and containing additives to overcome the residual effect of biocides and cleaning agents, should be selected. Additives inhibiting residual biocides and cleaning agents are an essential component of the culture medium.

STANDARD:

C.027 A written procedure designed to avoid potential contamination and/or cross-contamination from personnel and materials SoHO must be in place.

Explanation:

Entry of personnel, SoHO and materials should be done through airlocks by following specified procedures to avoid the direct flow of non-treated air into cleanrooms. Both airlock doors should not be open simultaneously. An interlocking system or a visual and/or audible warning system should be operated to prevent the opening of more than one door at a time.

Only the minimum number of personnel required for efficient processing should enter the processing areas. The need for additional persons to be present in processing areas should be taken into account during risk assessment when the procedure is being designed.

High standards of personal hygiene and cleanliness are essential. Changing and washing should follow a written procedure designed to minimise contamination of clean area clothing or transfer of contaminants to the cleanrooms. Wristwatches, make-up and jewellery must not be worn in clean areas. Outdoor clothing must not be brought into changing rooms that lead to Grade B and C rooms.

Required clothing should be chosen, based on the process and grade of the processing area. Minimum requirements modified from EU GMP Annex 1

STANDARD:

C.028 Gowning procedures for personnel must be validated at least in Grade A/B areas to ensure that gowning materials and protocols are adequate. Sampling points should be considered from the surface in several fixed sites on clothing:

- a. fingers of gloves;*
- b. facemask;*
- c. sleeve (forearm) of a suit;*
- d. front of the suit at chest height;*
- e. hood.*

STANDARD:

C.029 The cleaning process (both schedule and procedure) must be validated, and the validated cleaning process must be followed to achieve the required level of cleanliness

Explanation:

The cleaning validation should consider the influence of the time between processing and cleaning and the time between cleaning and processing to define how long the cleaning process can be delayed after processing and how long the cleaning process remains effective.

STANDARD:

*C.030 All cleaning procedures must be documented.
Cleaning must be done by personnel trained for the procedure, cleanroom environment, workflows and gowning.*

Explanation:

Appropriate disinfectants should be selected, based on the types of micro-organism found in the environment and an adequate risk assessment.

STANDARD:

C.031 In cases that the SoHO establishment accepts material for autologous use from donors infected with HIV, HBV or HCV separate processing must be done and validated cleaning procedures applied.

Explanation:

After processing, the surface should be decontaminated using disinfectant with specific label claims for blood-borne pathogens (e.g. HIV, HBV, HCV) or a freshly diluted bleach-based product in accordance with manufacturer's instructions, and the surface should be allowed to dry.

STANDARD:

C.032 Stringent biosafety requirements must be followed if processing SoHO from patients having known viral infections, e.g. hepatitis B virus (HBV), hepatitis C virus (HCV) or human immunodeficiency virus (HIV).

Explanation:

These should be determined by a documented risk analysis, considering the pathogenicity of the virus involved, and should consider:

- a. The potential requirement for a containment laboratory, having reduced air pressure with respect to adjacent rooms. It may be possible to temporarily generate a containment laboratory in a standard cleanroom facility by increasing the air pressure in the change rooms to result
- b. in the working room having reduced air pressure with respect to the last change room;
- c. The use of class II biosafety cabinets or isolators to handle contaminated material;
- d. The risk of cross-contamination of other SoHO processed at the SoHO establishment;
- e. Personnel safety, according to Directive 2000/54/EC on the protection of workers from risks related to exposure to biological agents at work;
- f. Handling and treatment of contaminated waste materials; any waste material generated during the process that could potentially be contaminated with viruses must be carefully handled and treated to inactivate any contamination. Ideally, the inactivation process should take place before the waste material leaves the processing laboratory. Where this is not possible, it should be placed in hermetically sealed containers before being removed from the laboratory for inactivation elsewhere

STANDARD:

C.033 Inactivation of prions must be considered if risk of prion contamination has occurred.

Explanation:

e.g. if SoHO from a Creutzfeldt–Jakob disease- positive donor have been processed or stored

STANDARD:

C.034 Handling and disposal of wastes must include appropriate collection, storage and transportation procedures according to applicable European, national and local regulation.

Processing Reagents

STANDARD:

C.035 The reagents used in processing must be of an appropriate grade for their intended use, be sterile (if applicable) and comply with existing national regulations and other relevant EU legislation (namely In Vitro Diagnostic Medical Devices Regulation).

Explanation:

Individual references should be taken into account, typically denoted on the labels of various reagents.

STANDARD:

C.036 Reagents that are not of appropriate grade must undergo risk assessment and validation to confirm that they are suitable for their intended purpose.

STANDARD:

C.037 Use of antibiotics during procurement, processing and preservation must be minimised, and, if used, information regarding the possibility of allergic reactions in the recipient must be included in the information provided to the end users.

STANDARD:

C.038 Whenever possible, reagents used for collection/procurement, processing, decontamination and preservation must be CE (Conformité Européenne) marked and/or of pharmacopoeia grade, if available.

Explanation:

Reagents not approved for human use may be used if an equivalent reagent of appropriate grade is not available, if the use has been authorised by national authorities (if applicable) and if the use is supported by risk assessment.

STANDARD:

C.039 The origin, characteristic conditions for storage (physical, chemical, microbiological) and expiry dates of reagents must be recorded.

STANDARD:

C.040 Critical reagents and consumables must have written specifications

Explanation:

These specifications should describe (when applicable):

- a. materials, including:
 - i. the designated name and the internal code reference;
 - ii. the reference (if any) to a pharmacopoeia;
 - iii. the approved suppliers and, if possible, the original manufacturer of the products;
 - iv. a specimen of printed materials;
 - v. certificate of compliance from the manufacturer.
- b. directions for sampling and testing, or reference to procedures;
- c. critical quality attributes, with acceptance limits;
- d. shelf life, storage conditions and precautions;
- e. the maximum period of storage permitted before re-examination.

Coding, Labelling and packaging

STANDARD:

- C.041 Upon receipt of the SoHO, the SoHO Establishment must assign a unique identification code to the material if this has not already been done at collection/procurement.*

Explanation:

This code can then be extended to identify the different products and batches of SoHO obtained during processing.

Example(s):

ISBT 128 or SEC are examples which could be used for this purpose

STANDARD:

- C.042 SoHO must be labelled at all stages of processing*

Explanation:

The label must include a unique identifier and, depending on the product, may also contain the following information:

- a. identification of the TE;
- b. type and characteristic of the product;
- c. batch or lot number (if applicable);
- d. recipient name (if applicable);
- e. expiry date (or retrieval date, when applicable).

The coded data must be entered in a register maintained for the purpose

STANDARD:

- C.043 SoHO processed for research purposes must be clearly identified as such on their packages and labels (e.g. 'FOR RESEARCH USE ONLY' or 'NOT FOR CLINICAL USE').*

STANDARD:

- C.044 If the SoHO are stored in liquid nitrogen, they must be double-bagged to prevent cross-contamination during storage or stored in validated high-security packaging especially designed for liquid nitrogen.*

STANDARD:

- C.045 The packaging materials must be stored in a clean area. In this case, the materials and the conditions under which packaging takes place must be carefully specified, assessed and approved before use.*

STANDARD:

- C.046 Primary packaging and transport containers used for SoHO must be validated for this purpose, and they must be suitable for use with human materials*

Explanation:

Selection of packaging, or a combination of packaging systems, should result in a sealed environment that prevents leaks.

Labels must be machine- printed for clarity. They should be printed with ink that does not run or otherwise become unreadable when exposed to water or other liquids. Labels must maintain integrity and remain attached to primary packages and transport containers at the storage temperatures.

All printed labels for primary packaging, secondary packaging and for documentation intended to accompany the SoHO product should be stored in access-controlled areas.

Quality Controls

STANDARD:

C.047 Tests and procedures must be carried out to measure, assay or monitor processing, preservation and storage methods, equipment and reagents to ensure compliance with established tolerance limits. Written procedures must be in place that govern quality control at key stages during processing

Explanation:

The written procedures should include as a minimum the test method, the sample size and the acceptance criteria.

The results of all tests or procedures should become part of the permanent processing record.

If in-process quality controls are undertaken in the processing area, they should be carried out so that there is no risk to the processing steps being followed

STANDARD:

C.048 The effectiveness of a decontamination or inactivation procedure must be shown for relevant micro-organisms in the SoHO preparation itself and not only in an aqueous solution.

STANDARD:

C.049 Non-conforming products must be identified and separated from conforming products.

Significant changes in processing protocols

STANDARD:

C.050 A documented change-control procedure must be followed before any significant change is implemented in processing.

Explanation:

This must be supported by a comprehensive risk assessment. The purpose of this is to ensure that the change is justified, is documented and will not affect the quality of the product. All relevant persons should be involved in evaluation of the change.

As a minimum, the following aspects of any change in processing should be evaluated:

- a. significance;
- b. effect on quality;
- c. need to update SOPs;
- d. need to re-validate the process;
- e. effects on quality-control (QC) analyses;
- f. need to inform, and be authorised by, regulatory authorities;
- g. need to train personnel;
- h. effect on risk analyses.

Packaging and Storage activities

STANDARD:

C.051 Management of packaging and labelling materials must include the following elements:

- a. there must be written specifications for all packages and labels used for SoHO;*
- b. there must be documented procedures describing the receipt, identification, quarantine, sampling, examination, testing, release and handling of both packaging and labelling materials;*
- c. a version control system must be in place to guarantee use of the current approved version. If a change of version occurs with regard to labels, inserts or packages, the actions needed to ensure that only the latest version is attached to the SoHO must be described in a written manner;*
- d. the suitability of packaging material, containers and labels for their intended purpose must be documented.*

STANDARD:

C.052 A maximum storage time with an expiry date for each type of SoHO and its storage conditions must be clearly defined.

Explanation:

The chosen maximum storage period for each individual type of tissue or cell should be validated, based on data from published studies, stability testing by the establishment or evidence-based facts (e.g. retrospective evaluation of the clinical results for SoHO supplied by the establishment), or it can be specified by national legislation.

When determining the maximum storage period, several factors should be considered. These include (but are not limited to):

- a. possible deterioration of the required properties of SoHO;
- b. risks related to microbiology;
- c. package integrity over time;
- d. expiry of storage solutions;
- e. stability at the storage temperature;
- f. overall risk assessment of quality assurance: donor evaluation, donor testing (kits), quality criteria (viability, functionality after thawing), regulations.

Example(s):

The expiration date of reagents is usually referred to the storage condition of the reagent itself and may condition the definition of the expiry date of the SOHO.

STANDARD:

C.053 Storage must be controlled and documented to ensure that the critical properties of the SoHO are maintained during storage and that cross-contamination or loss of functionality, efficacy, clinical effectiveness and traceability is avoided

STANDARD:

C.054 If an organisation entrusts one of the stages of storage to a third party, a written agreement is needed between the SoHO Establishment and the third party.

Explanation:

The SoHO Establishment must evaluate and select third parties based on their ability to meet the established standards of quality

STANDARD:

C.055 The maximum times from collection/procurement (or cardiac arrest, when applicable) until processing and storage must be defined to maintain quality, safety and clinical effectiveness of the SoHO

STANDARD:

C.056 Reference samples of SoHO for quality control must be stored under the same conditions as the SoHO themselves (e.g. cord blood reference samples).

STANDARD:

C.057 SoHO Establishments must have third-party agreements for transferring stored usable SoHO or for disposing of the unusable SoHO to another active SoHO establishment, including quality, safety and traceability and data.

STANDARD:

C.058 Refrigeration devices/incubators containing SoHO must be suitable for the intended use, and the procedures for monitoring such devices must be appropriate so that SoHO are maintained at the required storage temperature.

Storage Facilities

STANDARD:

C.059 Premises for storing SoHO, critical consumables and reagents must also be qualified, maintained and monitored

STANDARD:

C.060 Appropriate monitoring and alarm systems must be in place to indicate if conditions are approaching, or fall outside, predefined limits.

Explanation:

Storage requirements apply equally to interim storage of SoHO before transport to a processing facility. The functionality of the alarm systems must be checked regularly

STANDARD:

C.061 SOPs must define the actions to be taken and the organisation in place in response to alarms.

Explanation:

Storage requirements apply equally to interim storage of SoHO before transport to a processing facility. SOPs should be defined based on a documented risk analysis.

STANDARD:

C.062 Storage facilities must be cleaned according to a schedule.

STANDARD:

C.063 Facilities for storage must be dedicated to this activity, and must be designed, qualified and monitored to ensure appropriate conditions

Explanation:

SoHO establishments must have specific storage facilities/areas for the storage of SoHO.

Such storage areas must be:

- a. designated;
- b. located in a secure area, and access must be limited to authorised personnel;
- c. of sufficient capacity to allow orderly storage of the various status of SoHO, according to national requirements (i. in quarantine; ii. released for processing; iii. rejected; iv. returned; v. recalled; vi. for research use)
- d. covered by an adequate management system, ensuring clear identification of each status of SoHO;
- e. clean and dry, and maintained within an acceptable temperature range; and, where special storage conditions are required (e.g. specific temperature and/or humidity) these must be specified, maintained and monitored;
- f. cleaned, with a schedule based on the frequency of access by personnel and goods, by properly trained personnel and with approved products in order to keep the environmental bioburden under control.

Example(s):

The design of a cryostorage room must comply with applicable regulations and safety requirements of the relevant country.

(e.g. storage rooms equipped with liquid nitrogen tanks or equipment using liquid nitrogen)

STANDARD:

C.064 Items related to safety must include at least:

- a. good ventilation (capable of supporting emergency conditions in terms of operator and product safety);
- b. oxygen-level monitoring with a local audio and visual alarm;
- c. visual surveillance from outside;
- d. adequate space to contain the necessary freezers and tanks, including back-up systems;
- e. easy access to all the storage devices, with a smooth pathway to and from the facility for liquid nitrogen supply and for prompt removal and transfer of SoHO in case of emergency;
- f. personal protective equipment available for use, which may include items such as cryo-gloves, safety goggles, cryo-aprons and respirators;
- g. a specific SOP already in place to support the safety issues.

STANDARD:

C.065 A system to monitor all the alarms, including oxygen level in the room, the level of liquid nitrogen in the tanks, and the temperature of the tanks, is essential.

STANDARD:

C.066 When necessary, the ambient temperature of the storage area must be monitored.

STANDARD:

C.067 Dedicated training on nitrogen risks is required when storage in nitrogen for SoHO is in place

Explanation:

Training should include instruction on how to react to different alarms and to use personal protective equipment

STANDARD:

C.068 Storage facilities must have policies and SOPs for all processes that affect quality and safety.

STANDARD:

C.069 Organisations must have a dedicated area or equipment for quarantine (temporary storage) and a plan for back-up storage in the event that the primary storage area is unavailable.

STANDARD:

C.070 An inventorial audit of SoHO stored must be performed regularly.

STANDARD:

C.071 Continuous monitoring and recording of temperature, together with suitable alarm systems, must be employed on all incubators, storage refrigerators, freezers and liquid nitrogen tanks.

STANDARD:

C.072 Out-of-order equipment must be labelled accordingly

STANDARD:

C.073 A written sanitation programme must be available, describing the frequency and methods of cleaning. Additionally, a pest control system must be in place.

STANDARD:

C.074 The storage facility must be large enough for its intended purpose

Explanation:

The room should be in a dry, cool, well- ventilated place, free from unnecessary heat sources. Where mechanical refrigerators and freezers are utilised, suitable air conditioning systems may be required to dissipate excess heat.

The necessary air-conditioning capacity for the storage area should be calculated on the basis of the actual heat load of the equipment and the environmental factors.

STANDARD:

C.075 For security reasons, access to the storage facilities must be restricted to authorised personnel.

STANDARD:

C.076 In facilities where compressed gases are used, appropriate alarms for temperature control and low levels of oxygen must be in place, in case of liquid nitrogen leaks.

STANDARD:

C.077 In case of loss of electrical power, as a part of the general emergency plan, the storage facility must have an uninterrupted power supply (UPS) system linked to a backup generator for those devices where temperature cannot be maintained accordingly

STANDARD:

C.078 If storage is carried out based on the principles of GMP and defined in the in-house environmental hygiene programme, monitoring systems for storage rooms may need to be put in place. The frequency of monitoring, as well as the implementation of alarm limits, will depend on the degree of stringency needed and the principles of quality risk management.

Example(s):

Microbiological contact-plate monitoring may be performed to demonstrate the degree of cleaning of the room.

Another verification option would be to use a UV germ marker to set monitoring points to verify cleaning activities.

STANDARD:

C.079 The organisation of the storage room must allow circulation and manipulation around the cryogenic tanks.

STANDARD:

*C.080 Nitrogen Facilities must be clearly identified with pictograms indicating the dangers and also the location of personal protection equipment. The staff need to be specially trained and qualified for these working conditions.
Before entering the room, the staff must be able to ensure that ventilation is functioning correctly and be able to check the oxygen level.*

STANDARD:

C.081 Nitrogen Facilities must ensure that under normal operating conditions the minimum oxygen concentration is kept above a minimal level.

Explanation:

Continuous monitoring of the oxygen level must be ensured by detectors, checked and maintained to the supplier's recommendations. They must be placed in lower areas of the room in order to monitor any accumulation of nitrogen at floor level. The oxygen rate or alarm status must also be visible and audible outside the storage room.

Following nitrogen evaporation, leading to an oxygen level equal to or lower than 19 %, an alarm (visual and audible) must be activated, and staff should then leave the room and await normalisation of the oxygen level. The alarm should be connected to a continuous monitoring station allowing alerts for the staff working in the room and the rescue or assistance of staff, if necessary.

STANDARD:

C.082 Areas designated for separate storage of SoHO in process, under quarantine, and released for distribution must be established and controlled

STANDARD:

C.083 Where possible, SoHO must be stored in the vapour phase of liquid nitrogen, rather than by immersion.

Explanation:

If no alternative is available, SoHO immersed in liquid nitrogen should be double wrapped during storage or stored in a high-security primary container especially designed for liquid nitrogen (depending on the storage system, type of sample and after risk assessment)

STANDARD:

- C.084 The seals and the material employed must be qualified for their use at the designated storage temperature and for the conditions of use, to demonstrate that the packaging and labelling can retain their integrity under such conditions*

STANDARD:

- C.085 Periodical cleaning, a cleaning plan for the sanitation of the storage equipment must be implemented, depending on the type of equipment.*

Explanation:

During the cleaning process, a back-up unit should be used to provide the same safe conditions as the storage equipment. The emptying for cleaning and maintenance should be scheduled in advance and needs to be performed following an SOP

STANDARD:

- C.086 For periodical cleaning, a cleaning plan for the sanitation of the storage equipment must be implemented, depending on the type of equipment. During the cleaning process, a back-up unit must be used to provide the same safe conditions as the storage equipment. The emptying for cleaning and maintenance must be scheduled in advance and needs to be performed following an SOP.*

STANDARD:

- C.087 All human SoHO that are stored before having determined their suitability must be kept under quarantine storage*

STANDARD:

- C.088 SoHO Establishment must operate a system that identifies SoHO throughout any phase of processing and clearly distinguishes released products from quarantined and discarded products.*

Explanation:

An SOP must describe how to categorise quarantined and released SoHO.

Example(s):

To maintain physical separation, specific areas or storage devices (or secured segregation within the device) must be defined for SoHO in quarantine, for SoHO that must comply with special criteria and for SoHO that have been released; a separate area must be dedicated to the storage of medium and other materials used during the process of preparation

STANDARD:

- C.089 There must be a documented policy for disposal of SoHO that are unsuitable for clinical use*

Explanation:

Records must include details of date and involved personnel, with method of and reasons for disposal. The material must be handled appropriately and disposed of in a manner compliant with local guidelines on control of infection. Human SoHO and other hazardous waste items must be disposed of in such a manner as to minimise the hazards to the TE's personnel or the environment, and must be in conformity with applicable European, national and local regulations.

Example(s):

Not meeting quality criteria, withdrawal of permission from donor, death of autologous donor.

PART D. DISTRIBUTION

Transport after release

STANDARD:

D.001 Critical transport conditions, such as temperature and time limit, must be defined to ensure maintenance of the required properties of SoHO

Explanation:

If the SoHO require specific environmental conditions, the capacity of the transport container to maintain the required environmental conditions, and the length of time that these conditions can be maintained by the transport container, must be determined by validation and documented.

When the transport device does not allow the temperature conditions to be maintained over time, a time limit must be validated to guarantee that the storage conditions during transport do not affect the quality of the SoHO.

Example(s):

For instance, if liquid nitrogen is used to maintain very low temperatures, the dry-shipper must contain sufficient absorbed liquid nitrogen to maintain the storage chamber temperature $< -140^{\circ}\text{C}$ for a defined period of time, at least 48 h beyond the expected time of arrival at the receiving facility. In cases where the SoHO during transport could be exposed to a wide range of outdoor temperature (e.g. winter versus summer) the cycling temperature validation profiles should be used for validation of the transport container.

STANDARD:

D.002 The SoHO Establishment must validate the best recommended shipping temperature for their products. Shipping container must be able to maintain this environment for an appropriate amount of time during transport, according to the worst cases scenario

Explanation:

The entire distribution chain must be validated appropriately, including the equipment used, to ensure the maintenance of critical transport or shipment conditions.

STANDARD:

D.003 Appropriate control of transport and transport conditions, appropriate handling and preparation before use and full traceability must all be maintained

Explanation:

Transport procedures should be validated according to the “worst case scenario” to ensure the maintenance.

Example(s):

The place, date and time of pick-up and delivery (including time zone where relevant) and identity of the persons handing over and receiving the SoHO must all be recorded, and this record should be maintained in the TE from which the SoHO are distributed.

Any transportation must be accompanied by specific documentation attached to the package

Where temperature control is critical, transport validation is mandatory (for all extreme conditions), and additionally, data loggers could be used to monitor temperature during transport or shipment, with data downloaded from the device providing a graph to show that temperature was within the acceptable range at all times. Temperature indicators can be also used to indicate exposure to extremes of temperature.

STANDARD:

D.004 The SoHO establishment must implement appropriate measures, such as instructions for use and traceability record labels, which are provided to the clinical user in order to ensure product quality and traceability down to the recipient.

Explanation:

Some national standards require the organisation responsible for human application (ORHA) of SoHO to provide the supplying SoHO establishment with details of the patient to whom the SoHO were clinically applied.

Distribution to the patient for use without direct supervision of a health professional requires particular attention to instructions for storage and use and should be carried out only if it is the only available option.

Evidence:

Maintenance of quality and traceability is achieved by providing clear and detailed written instructions for users

STANDARD:

D.005 Containers/packages must be secured and labelled appropriately.

Explanation:

Packaged SoHO must be examined visually for appropriate labels, expiry date, container integrity and security, and any evidence of contamination prior to being dispatched

STANDARD:

D.006 Written agreements must be in place for the shipment of SoHO.

Explanation:

In EU member states a written agreement must be signed between the shipping company and the SoHO Establishment to ensure that the required conditions will be maintained.

Evidence:

This document must describe what should happen if the SoHO are damaged or lost during shipment and must cover a requirement that any related serious adverse events should be identified and reported to the Health Authorities

STANDARD:

D.007 Distribution for clinical application must be restricted to hospitals, physicians, dentists or other qualified medical professionals and must comply with all applicable national regulations. There must be a formal service-level agreement (SLA) or contract in place between the supplying TE and the ORHA.

Explanation:

These written agreements should be signed, dated and reviewed regularly (as defined by the parties concerned), but sooner if changes are required. They must comply with relevant laws and regulations. Where an ORHA and the supplying TE are within the same healthcare institution, responsibilities should be specified in the overall quality-system documentation.

Example(s):

Service-level agreements should include:

- a. contact details for relevant persons in both parties, including the TE's Responsible Person (RP);
- b. procedures for ordering, including the method of assuring relevant quality and quantity parameters of ordered SoHO;
- c. procedures for the delivery of SoHO, including liability for transport;
- d. a statement that storage and preparation of SoHO for human application at the ORHA must comply with all relevant and specific instructions provided by the TE, including adherence to expiry dates;
- e. procedures at the ORHA for the lawful disposal of unused SoHO or remnants of SoHO after human application;

- f. procedures, if permitted, for the return of SoHO to the TE, or to use for research;
- g. responsibility for maintaining traceability and biovigilance, including procedures for the timely reporting and investigation of adverse reactions and adverse events, including 'near misses', and procedures for the management of tissue and cell recalls and look-backs;
- h. procedures, where permitted, for reporting of relevant clinical outcome data relating to the quality, safety and efficacy of the applied SoHO by the ORHA to the TE;
- i. the option for SoHO Establishment and ORHA to conduct an audit of the other party.

STANDARD:

D.008 SoHO Establishment must have a documented policy on SoHO release that describes which specifications must be met and when, how and by whom these are verified.

Explanation:

Specifications must include all criteria considered by the SoHO Establishment to be essential for the safety and quality of the SoHO. In general, only when all specifications have been evaluated and met can the SoHO be distributed for clinical application.

STANDARD:

D.009 There must be an SOP that details the specifications, circumstances, responsibilities and procedures for the release of SoHO.

Explanation:

Before any SoHO are released, all relevant records (including current declaration forms, donor records, medical records, processing and storage records, and post-processing quality- control test results) must have been reviewed, approved and documented as acceptable by an authorised and trained person according to the relevant local SOP and national regulations.

Example(s):

At the time of release, donor records and SoHO-processing records must be reviewed to ensure that the material is suitable for clinical use and implantation.

The review should include:

- a. approval of donor eligibility by the responsible person (RP) or designated person;
- b. consideration and approval of the processing and storage record (including environmental monitoring records);
- c. final evaluation of the label and container to ensure traceability, accuracy and integrity;
- d. results of screening tests on incoming material and in-process controls;
- e. specifications for final release of SoHO based on testing results used to determine final release (e.g. quality controls such as viability or cells count, microbiology test results, biological activity);
- f. all the same checks if the SoHO are designated for autologous use;
- g. in case of deviating test results, the decision of the RP and the treating physician whether the SoHO can be used, but in any case the final decision has to be justified and documented.

There must be a documented system in place, supervised by the RP, for ratifying that SoHO meet the appropriate specifications for quality and safety. The RP, or personnel designated by the RP, must register (in writing or digital format) the review and fulfilment of all legal requirements, SoHO specifications and quality-release criteria as

defined by the SoHO Establishment, thereby releasing the SoHO for storage in an inventory of SoHO that are available for human application. If release cannot be approved, the SoHO must be discarded or can be made available for research/educational use, if a specific consent for research/educational use was given.

STANDARD:

D.010 Released SoHO must be clearly distinguishable (by labelling and/or packaging whenever possible, or by any other means (e.g. computerised systems) and preferably be physically separated from quarantined and discarded tissues.

STANDARD:

D.011 SoHO Establishments must have procedures in place for the management of requests for SoHO. The rules for allocation of SoHO to certain patients or healthcare institutions must be documented, and made available in appropriate circumstances, in the interests of transparency.

Explanation:

The allocation of SoHO should be guided by clinical criteria and ethical norms. The allocation rules should be equitable, externally validated and transparent.

STANDARD:

D.012 The SoHO Establishment must provide clinical users with instructions for handling and using the SoHO.

STANDARD:

D.013 Exceptional release must be based on a risk–benefit analysis taking into consideration the alternative options for the patient and the consequences of not providing the SoHO, and this analysis requires documented informed consent by the treating physician

Explanation:

In exceptional circumstances, an ORHA may agree with a TE that SoHO that do not meet the normal release criteria can be applied in a specific individual on the basis of a risk–benefit analysis, taking into consideration the alternative options for the individual and the consequences of not providing the SoHO. The risk assessment should be documented and shared with the treating clinician about the reason for the exceptional release of SoHO. The TE's RP or nominated deputy/individual should liaise with the recipient's clinician to discuss the exceptional release so that the treating clinician can make a decision by performing a risk–benefit analysis for the intended recipient. These discussions and conclusions must be documented. The treating clinician must inform the recipient, where possible, as part of the normal consenting procedure of the intention to use SoHO under exceptional release

STANDARD:

D.014 A documented risk assessment approved by the RP must determine the fate of all stored SoHO following the introduction of any new donor selection or testing criterion or any significantly modified processing step that enhances safety or quality.

PART E. REGISTRIES AND VIGILANCE

Clinical Investigations and Biovigilance

STANDARD:

E.001 SoHO Establishment is expected to have procedures in place to notify, without delay, other SoHO Establishments or the relevant Health Authority of all available information about:

- a. knowledge of deviations from approved procedures that have occurred or that are suspected to have occurred and which could have affected the quality and/or safety of collected/procured SoHO and that could have resulted in a SARE;*
- b. any serious adverse reaction in a living donor that may influence the quality and safety of the SoHO collected/ procured;*
- c. any serious adverse event during procurement that may influence the quality and/or safety of SoHO.*

STANDARD:

E.002 SoHO Establishment must have a policy for introducing new or novel SoHO/therapies into clinical use

Explanation:

Where novel SoHO are supplied, the extent of clinical follow-up needed to evaluate the efficacy of the applied SoHO must be defined based on a risk assessment and in agreement of the health professionals responsible for the clinical application, it must also be agreed between the Health Authority, SoHO Establishment and ORHA

Evidence:

This policy should be defined in SOP(s) and/or associated Quality Management Documents.

It should include the definition of procedures associated with an eventual authorisation request; the definition of clinical data associated with the use of novel SoHO.

STANDARD:

E.003 The level of clinical follow-up must be determined by risk assessment using standard methodology such as the EuroGTP II tool.

Explanation:

It should consider any residual risk for recipients/patients, which could not be mitigated by the pre-clinical studies.

The requirements of the clinical evaluation and the extent of plan for collecting clinical data should be proportional to the remaining level of risk.

STANDARD:

E.004 SARE must be reported to the Health Authority/ies, in a timely efficient manner

Explanation:

There should be a SOP to investigate and report SARE reported by Health professionals at ORHAs, and/or other personnel involved in the SoHO supply chain.

SoHO Establishments should provide clear instructions on how to report SARE, preferably using standardised documentation.

Example(s):

In general, any suspected SARE should be reported immediately to the SoHO Establishment that supplied the SoHO, before it is confirmed or investigated, to enable the SoHO Establishment to take appropriate

precautionary actions to prevent harm to other recipients and to involve the SoHO Establishment in the investigation process.

An additional important source of information on possible adverse outcomes and their frequency may also be based on specific types of SoHO and their specific applications, e.g. registries, if they exist.

STANDARD:

E.005 Where the collection of clinical follow-up data is proposed, recipients may need to provide consent for the sharing and secondary use of their data in accordance with national legislation and guidance.

Explanation:

In the EU, the General Data Protection Regulations (GDPR, Regulation EU 2016/679) provide certain exemptions from the need for consent for the collection and use of such data under Articles 6.1 (e) and 9.2 (h). However, recipients must be informed about the collection and use of their clinical data and, although they do not need to give consent, they do have the right to refuse to allow their data to be collected and used.

STANDARD:

E.006 The extent and duration of the routine clinical follow-up must, where possible, be standardised for each SoHO product and application.

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