



ACCREDITATION MANUAL – Standards for Intestinal Microbiota

(Chapter O)

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



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INTRODUCTION

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

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

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

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

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

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

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

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

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

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

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

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

Disclaimer

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

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

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

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

ABBREVIATIONS[‡]

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

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

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

DEFINITIONS[§]

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

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

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

INDEX/STANDARDS STRUCTURE

GENERIC STANDARDS FOR SoHO ACTIVITIES:	A. DONOR SELECTION & DONATION:	A.1. LIVING DONATION	F. OCULAR TISSUES
		A.2. DECEASED DONATION	G. AMNIOTIC MEMBRANE
	B. COLLECTION		H. SKN
			I. CARDIOVASCULAR
	C. PROCESSING, STORAGE AND RELEASE OF SoHO		J. MUSCULOSKELETAL
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	D. DISTRIBUTION		L. ADIPOSE TISSUE
			M. HUMAN MILK
	E. REGISTRIES AND VIGILANCE		N. BLOOD COMPONENTS FOR TOPICAL USE OR INJECTION
			O. INTESTINAL MICOBIOTA

PART M.1.: Intestinal Microbiota

Recruitment of potential donors, identification and consent

STANDARD:

O.1.001 Anonymous donors must be used, to ensure anonymity and independence between donor and recipient.

Explanation:

Promotion of altruistic unpaid donation of faecal microbiota by means of advertisement or public appeal may be undertaken in accordance with domestic regulations.

Anonymous donors are preferred to maintain the ethical separation between the donor and recipient and maintain the donation as an impartial act of altruism.

STANDARD:

O.1.002 In addition to the generic donor selection criteria, potential faeces donors must be screened based on the criteria defined in the EDQM Guide

Explanation:

The criteria to select potential donors are listed in the EDQM T&C Guide, and aim to identify subjects suffering from recent or chronic diseases or who take drugs that may alter the donor microbiota

STANDARD:

O.1.003 Faecal microbiota transplantation (FMT) preparations for severely immunocompromised patients must be made with additional safety precautions. Matching the Cytomegalovirus (CMV) and Epstein–Barr virus (EBV) status of donor and recipient or using CMV-negative donors may be considered. In particular, seropositive donors (IgM and/or IgG) must not be matched with seronegative patients.

STANDARD:

O.1.004 Once a donor has been approved, he or she must complete a second short questionnaire before each donation to assess any event that may have occurred between donor approval and donation

Explanation:

The EDQM T&C Guide provides guidance for this questionnaire

STANDARD:

O.1.005 Complete donor screening based on blood and faecal analyses must be repeated at minimum every 3 months

STANDARD:

O.1.006 The donation period must have a defined maximum duration, not exceeding 3 months, and must start and end with a complete donor screening

Explanation:

Complete post-donation period re-screening before any use of the preparations allows for an exemption from blood screening at each donation.

Blood tests pertaining to the close-out screening should be performed a minimum of 4 weeks after the last donation thus taking incubation times into account.

If donor screening is performed as recommended by the EDQM T&C Guide, direct testing of each preparation is not mandatory. It may, however, be necessary according to local regulation, or in severely immunocompromised patients.

STANDARD:

O.1.007 FMT preparations that have been processed during a donation period must be put under quarantine until the repeat donor screening results are approved.

Collection

STANDARD:

O.1.008 Donors must be able to deliver their donation to the FMT facility within 2 hours following defecation.

Explanation:

Preferably, defecation would take place at the FMT facility, but in most cases, faeces are collected by the donor at his or her home.

If the duration from defecation to delivering the faeces to the tissue establishment is longer than 30 minutes, temporary storage at 2-8 °C is preferred because faecal storage without stabilisation buffer significantly changes taxa abundances from 30 minutes onwards.

STANDARD:

O.1.009 The processing facility must provide sterile faecal containers validated for transportation of human material.

Processing, Preservation and Storage

STANDARD:

O.1.010 Visual inspection of the donor faeces must be undertaken to document stool consistency and to confirm the absence of blood and urine.

STANDARD:

O.1.011 To preserve the donated faecal microbiota, stool must be processed within 6 hours of defecation

STANDARD:

O.1.012 A biosafety cabinet must be used to protect personnel from unpleasant odours and contamination during manufacture.

STANDARD:

O.1.013 Prior to the processing procedures, the designated spaces and non-disposable equipment must be sterilised, if possible using measures effective against sporulating bacteria

STANDARD:

O.1.014 Protective gloves and facial masks must be used during preparation.

STANDARD:

O.1.015 If a faecal donation cannot be processed immediately, it must be stored at 2-8 °C until initiating the procedures

STANDARD:

*O.1.016 Preparation of faecal preparations under aerobic conditions is considered suitable when preparing FMT for use in patients with *Clostridioides* (formerly *Clostridium*) *difficile* infection (rCDI), because anaerobic processing does not increase clinical cure rate.*

STANDARD:

O.1.017 It is preferable to use ≥ 50 grams of crude faeces per FMT preparation

STANDARD:

O.1.018 Donor faeces for liquid FMT preparation must be homogenised with cooled, sterile 0.9 % saline, using a blender, smasher or stomacher bag.

Explanation:

The amount of added saline depends on the viscosity required for clinical application

STANDARD:

O.1.019 Donor faeces intended for infusion may be sieved or centrifugated to remove debris and thereby prevent clogging during administration.

STANDARD:

O.1.020 Donations for encapsulated FMT may undergo further centrifugation steps to concentrate the donated sample and reduce the required number of capsules.

STANDARD:

O.1.021 Before freezing, glycerol must be added as a cryoprotectant up to a final concentration of 10 % for liquid-based preparations.

Explanation:

The amount of glycerol used for microbiota cryopreservation has no effect on the recipient

STANDARD:

O.1.022 For lyophilisation of FMT preparations, a lyoprotectant must be added in order to protect the faecal microbiota during the freeze-drying process.

Example(s):

Examples of lyoprotectant: trehalose, sucrose or skimmed milk

STANDARD:

O.1.023 Preparations must be stored at -60°C to -80°C . Soon-to-be-used preparations may be stored at -20°C in relation to clinical application. Freeze dried preparations may be stored at room temperature, but storage at -60°C to -80°C prevents moisture permeation.

STANDARD:

O.1.024 The preparation labels must include a unique donor code and number, processing and expiration date, volume and storage instructions.

STANDARD:

O.1.025 The following criteria must be followed for the definition of expiration dates:

- *Storage at -80°C for up to 24 months*
- *Storage at -20°C for up to 4 weeks*
- *Storage at $2-8^{\circ}\text{C}$ for up to 24 hours*
- *Storage at ambient temperature for up to 6 hours*
- *Thawing may be done overnight at 2°C to 8°C or at ambient temperature for up to 6 hours.*
- *Thawing time from -20°C at ambient temperature is usually 15 minutes*

Distribution

STANDARD:

O.1.026 Distribution of faecal preparations from a SoHO establishment to an FMT service requires a written agreement between the SoHO establishment and the FMT service in which each party's responsibilities are described.

Explanation:

The faecal preparation must be ordered by a clinician or other authorised person

Prior to distribution, the third party must confirm that it is in possession of sufficient facilities to safely conduct an FMT. Clinical administration and patient follow-up is the responsibility of the treating physician.

STANDARD:

O.1.027 Distribution of FMT preparations must be performed using dry-ice shipment through a certified courier service. If preparations are to be used immediately following transport, this may be done at 2-8 °C.

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