SoHO Coordination Board (SCB)

Inspection guidelines (version 1.0)

Inspection Guidelines for EU Competent Authorities responsible for the inspection of SOHO entities and SOHO establishments under the SOHO Regulation (EU) 2024/1938

These Guidelines have been developed by the Working Group on Inspections of the SoHO Coordination Board (SCB).

These guidelines are based on the former VISTART Inspection Guidelines, which were developed under work package 6 of the VISTART Joint Action. One of the objectives of the VISTART Joint Action was to establish a common framework for the conduction of inspections of blood and tissue establishments across Member States. The former 'Inspection Guidelines for EU Competent Authorities Responsible for the Inspection of Blood and Tissue Establishments' (the Guidelines), were set out to achieve this objective.

On 17 July 2024, a new Regulation on standards of quality and safety for substances of human origin intended for human application was published in the Official Journal of the EU. The Regulation was adopted by the Council on 27 May 2024 and approved by the European Parliament on 24 April 2024.

The new Regulation required an adjustment of the guidelines. All the insights and recommendations of the former VISTART Guidelines have been incorporated into these new SoHO Guidelines. Additional recommendations developed in the past years have been added, and the Guidelines are written in line with Regulation (EU) 2024/1938.

These Guidelines have been approved by the SoHO Coordination Board before their publication.

In these Guidelines, the use of the term 'shall' indicates a requirement of applicable legislation (mostly the Regulation (EU) 2024/1938) and the use of 'should' indicates a recommendation. In the context of these guidelines, should is used.

Throughout the document, the term SoHO entities is used, which also includes SoHO establishments, as these are also still SoHO entities according to the definitions of Regulation (EU) 2024/1938.

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Abbreviations

ATMP	Advanced Therapy Medicinal Products
CA	Competent Authority
CAPA	Corrective and Preventive Actions
CO	Collection Organisation
EDQM	European Directorate for the Quality of Medicines and Health Care of the Council of Europe
EMA	European Medicines Agency
EU	European Union
FMEA	Failure Mode and Effect Analysis
GMP	Good Manufacturing Practice
HACCP	Hazard Analysis and Critical Control Point
IFA	Illegal and Fraudulent Activity
ISO	International Standards Organisation
ISE	Importing SoHO Establishment
IVD	In Vitro Device
IVF	In Vitro Fertilisation
MAR	Medically Assisted Reproductive Technology
MD	Medical Device
MS	(European Union) Member State
MIRCA	Microbiological Risk of Contamination Assessmen
PIC/S	Pharmaceutical Inspection Convention / Pharmaceutical Inspection Cooperation Scheme
PO	Procurement Organisation
PPA	Preparation Process Authorisation
PPD	Preparation Process Dossier
QM	Quality Manager
QMS	Quality Management System
RCA	Root Cause Analysis

RP	Responsible Person
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SARE	Serious Adverse Reactions and Events
SCB	SoHO Coordination Board
SEC	Single European Code
SMF	Site Master File
SoHO	Substance of Human Origin
SOP	Standard Operating Procedure
3CS	Third Country Supplier

1 Introduction - Aim and Scope of the Guidelines

The primary objective of the Guidelines is to provide competent authorities (CAs) with a common framework for conducting inspections of SoHO entities (SoHO-establishments, SoHO entities, third parties or third country suppliers).

Transfusion, transplantation, and medically assisted reproduction are important areas of healthcare across the EU and these Guidelines will contribute to further laying the foundations to the implementation of systems for inspection and supervisory activities that are potentially compatible with each other, also with respect to the field of different SoHO. The Guidelines will facilitate a harmonised approach to inspections across the EU, resulting in increased confidence in the mutual recognition of national inspections.

A secondary objective is to provide high level guidance on the key procedures and documents necessary for the following tasks:

- General governance and quality management principles for CAs;
- Key procedures and documents for authorising SoHO establishments[1];
- Preparation Process Authorisations;
- Scheduling, preparation, conduct and follow-up of inspections;
- Recruitment, training and management of inspectors;
- Oversight of import and export;
- Assessing vigilance procedures.

[1] The words 'authorise or authorisation' are used in these Guidelines to also mean accreditation, designation or licensing.

2 General Governance and Quality Management Principles for Competent Authorities

References

- Designation of SoHO competent authorities (art. 5).
- Independence and partiality (art.6).
- Transparency (art. 7).
- General responsibilities and obligations of SoHO competent authorities (art. 8).
- Delegation of certain SoHO supervisory activities to other bodies (art. 9).
- SoHO rapid alerts (art. 34).
- Commission controls (art. 71).
- General functionalities of the EU SoHO Platform (art. 74).
- Confidentiality (art. 75).

The Regulation (EU) 2024/1938, repealing Directives 2002/98/EC and 2004/23/EC, establishes measures that set high standards of quality and safety for all substances of human origin (SoHO) intended for human application and for activities related to those substances. It ensures a high level of human health protection, in particular for SoHO donors, SoHO recipients and offspring from medically assisted reproduction, including by strengthening the oversight activities provided by MS and guaranteeing the continuity of supply of critical SoHO.

According to Regulation (EU) 2024/1938, SoHO competent authorities shall be responsible, within their territory, for SoHO supervisory activities in order to verify the effective compliance by:

- SoHO entities with the requirements set out in this Regulation; and
- SoHO preparations with their corresponding authorisation.

SoHO competent authorities should perform SoHO supervisory activities regularly, on the basis of a risk assessment and with appropriate frequency, on SoHO entities and activities governed by this Regulation.

The frequency of SoHO supervisory activities, and the mode in which inspections are carried out, shall be established by the SoHO competent authorities. The degree of control should be adjusted to the risk and to the level of compliance expected in different situations, including the possible violations of this Regulation committed through fraudulent or other illegal practices, and be based on previous compliance history of entities. Accordingly, the likelihood of non-compliance with any provisions of the Regulation should be taken into account when scheduling SoHO supervisory activities.

The following chapter provides guidance on the key policies and procedures that are essential to managing effective licensing and CA inspection function and that should form part of a CA Quality Policy and Manual.

2.1 Governance

2.1.1 Independence and Impartiality

When performing their tasks and exercising their powers, SoHO competent authorities shall act independently and impartially, in the public interest and free from any external influence, such as political influence or industry interference. The application of these principles is vital in fostering public and stakeholder confidence in the fairness and objectivity of the procedures and decisions of the CA. The organisational structure of the CA, supported by systems and processes, should ensure adherence to the principles of independence and impartiality, which the CA should be able to demonstrate.

CAs should also ensure that employees or external persons or organisations are not able to improperly influence inspections or the decision-making processes. Rules for professional conduct, ethics and conflict of interest declarations should be clearly defined and managed, and conflict of interest should be regularly updated. To ensure impartiality and objectivity, CAs should implement a rotation policy (where possible) for inspectors, as there is a risk of familiarity when the same individuals inspect the same entities over time.

The relationship of the CA with other CAs, external organisations or other directorates within the CA should be described where relevant, e.g. when another organisation conducts activities on its behalf ('delegated bodies', article 9) or provides data that may be used to influence decisions.

2.1.2 Transparency and publication of supervisory activities

SoHO competent authorities shall carry out the SoHO supervisory activities they have been made responsible for, in a transparent manner. They shall lay down in their internal rules practical arrangements for implementing the transparency rules of the Regulation (EU) 2024/1938.

CAs shall:

- Carry out SoHO supervisory activities transparently at least by complying with publication requirements in the Regulation:
    - List of registered entities;
    - List of authorised SoHO establishments;
    - Suspension or withdrawal of a SoHO preparation authorisation;
    - Suspension, or cessation (in part or in full) or withdrawal of SOHO establishment authorisation;
    - The suspension or cessation of any other procedure or activity of a SoHO entity;
    - Annual aggregated report of activity data for their SoHO entities;
    - Annual summary of confirmed SAR or SAE notifications;

    - Communicate to the general public when applicable/relevant information in relation to SAREs which pose a risk to public health.
- Publish enforcement decisions and reasons in cases of non-compliance or serious risk to health, with due regard to confidentiality laws; in cases where a SoHO entity does not comply with the Regulation, or there is a serious risk to the safety of SoHO donors, recipients or offspring from MAR or to public health.

The EU SoHO Platform, which has been developed under the Regulation (EU) 2024/1938, contributes to improving transparency of reporting about SoHO supervisory activities and to the exchange of information between relevant parties, including decisions on the regulatory status of substances, products or activities. The EU SoHO Platform should also serve as a reliable source of information for the public regarding the work of the SCB, SoHO national authorities, expert bodies, including the EDQM and the ECDC, and SoHO entities. The SoHO Platform should be further used for the sharing of best practices documented and published by the SCB on SoHO supervisory activities.

Further information in relation to the data available on the SoHO platform can be found in section 2.2.9 Exchange of information between EU MS/Competent Authorities.

2.1.3 Personnel and Organisation

SoHO CAs shall have, or have access to, a sufficient number of suitably qualified and experienced personnel, human and financial resources, operational capacity, and expertise, including technical expertise, to carry out the SoHO supervisory activities they have been made responsible for, efficiently and effectively.

SoHO CA shall have appropriate and properly maintained premises and equipment to ensure that the personnel can perform their SoHO supervisory activities safely, efficiently and effectively.

The responsibility, authority, and reporting structure of a CA's inspection function should be clearly defined and documented in organisational charts and should be supported by written job descriptions for each member of the staff. The job description should as a minimum empower inspectors (and assessors and vigilance officers if they are part of the inspectorate) to:

- Inspect SoHO establishments and if necessary, entities, third parties or third country suppliers (only for inspectors);
- Evaluate and verify the procedures and activities carried out by the establishment, entities, third parties or third country suppliers that are relevant to the requirements of Regulation (EU) 2024/1938;
- Examine any documents or other records relating to the processes.

2.2 Quality Management

CAs shall have a quality management system or standardised documented procedures in place for the SoHO supervisory activities they have been made responsible for that include a plan for continuity of their activities in the case of crisis situations that impede the normal performance of their tasks.

CAs should define, implement, and maintain a quality policy, which sets out the CA's approach to the management of its licensing and inspection functions. As a minimum, the quality management system should contain documented procedures and policies on the following activities:

- Planning (risk based), scheduling, conducting and reporting of inspections;
- Documentation of roles, responsibilities of personnel and organisation;
- Selection, training and competence assessment of inspectors, assessors and vigilance officers;
- Handling of serious adverse events and reactions (SAE/SAR) and recalls, including communication flows;
- Identification of illegal and fraudulent activities;
- Processes for authorising establishments;
- Processes for revocation or suspension of an establishment's authorisation;
- Processes for authorising SoHO preparations.

These documented procedures and policies should undergo regular review and improvement.

2.2.1 Quality policy and manual

CAs should have in place a Quality Policy, which defines the quality objectives of the CA (Figure 1).

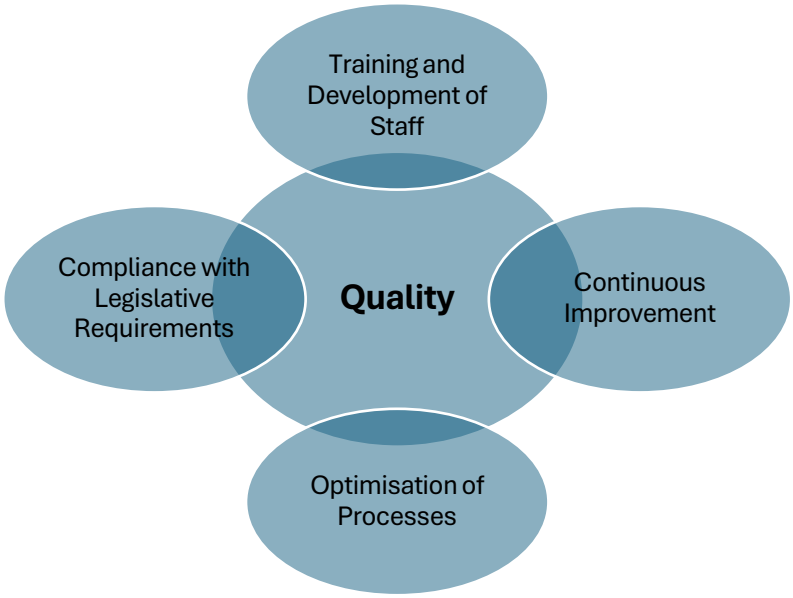


Figure 1: Examples of quality policy objectives.

The Quality Policy should be supported by a Quality Manual or other document which describes the quality management system and outlines the roles and responsibilities of the personnel involved in the operation of the system. The Quality Manual should include at least, or refer to, the procedures which define the activities of the CA and the arrangements for maintaining and improving the quality management system.

2.2.2 Documentation and change control

CAs should establish and maintain a document control system to manage all documentation relevant to the functions of its inspectorate. Relevant documentation includes: the standards used for inspecting entities, quality manual, policies, procedures (e.g. procedures for performing inspections), guidelines and any documents of external origin such as Regulations and Directives which direct the activities of the inspectorate or influence the quality of its operations.

The documentation system should ensure that any changes to documents are made in a controlled manner, are properly approved and are distributed to the appropriate personnel.

A policy for the control of documents and records should be implemented to ensure the maintenance of confidential information. A system should be in place for the maintenance and retention of records relating to the activities of the inspectorate e.g. those relating to inspections, follow-up actions and decisions relating to authorisation, designation, accreditation or licensing of an establishment. There should be a records' retention policy that describes what records should be retained and for how long.

Records containing confidential information should be stored securely with controlled access to ensure that confidentiality is maintained.

Clear procedures should be developed and implemented with regards to the archiving of inspection related documents to ensure traceability of actions and decisions.

2.2.3 Internal and external audit

A system should be established for performing and documenting periodic internal audits of the inspectorate's activities to assess compliance with the requirements of the quality management system.

The procedures for selecting internal auditors and conducting audits should ensure the objectivity and impartiality of the audit process. Personnel responsible for the systems and processes being audited should ensure that actions are taken without undue delay to implement improvement action plans resulting from the audit. Follow-up actions should include verification of the actions taken and reporting of the results to assess whether they have achieved the intended outcomes.

The quality management system should also be subject to auditing by an external body. These Guidelines recommend that CAs obtain certification by an official body. Alternatively, CAs may participate in a voluntary programme of inter-MS auditing. External audits will provide an objective level of confidence that the activities being undertaken are in accordance with rigorous standards and clearly defined procedures.

2.2.4 Commission controls

The Commission shall perform controls to confirm whether MSs effectively apply the requirements relating to:

- SoHO competent authorities and delegated bodies;
- The SoHO supervisory activities carried out by SoHO CAs and delegated bodies;
- The notification and reporting requirements of the SoHO Regulation.

2.2.5 Quality improvement

There should be a periodic review of the operation of the quality management system to identify opportunities for continual improvement of systems and processes.

To ensure that the inspection system is functioning effectively and to identify areas for improvement, the performance of the inspectorate should be monitored by establishing a set of quality indicators related to its activities, *e.g.*:

- Number and type of inspections conducted per year (and how many were not conducted according to planning);
- Number of establishments licensed per year (if applicable);
- Average time from inspection to final report;
- Average time taken to authorise a preparation process (if applicable);
- Average time taken to authorise another process (for example licencing a new establishment, licencing changes in existing establishments);
- Average time taken to handle notifications of SAE/SAR.

A year-on-year analysis of non-compliances identified during inspections and a review of the serious adverse events and reactions reported should be performed where possible, to reveal emerging trends and to inform inspection scheduling to ensure that the inspectorate's resources are targeted at the areas of highest risk. A summary report of the analysis of non-compliances may be made available to establishments as an educational tool and to promote improvements.

The performance of inspectors should also be reviewed using performance indicators, for example:

- Number of reports issued within the prescribed time frame;
- Adherence to inspection procedures;
- Clarity of inspection reports;
- Depth of scientific, technical, and regulatory review during the conduct of an inspection;
- Assessment of effectiveness and consistency of inspections;
- Consistency in classification of non-compliances;
- Peer review of inspection reports;
- Periodic calibration exercises between inspectors.

Further improvements to inspection processes and the performance of inspectors may be identified by seeking feedback from establishments. This could be achieved by providing establishments with a feedback form following an inspection or alternatively, an inspection feedback survey could be conducted on an annual basis. The results of the feedback should be used to inform the inspector training and development programme as well as driving improvements to the overall management of inspections.

2.2.6 Management of risks arising from the activities of an inspectorate

CAs shall include in the QMS a plan for continuity of their activities in the case of crisis situations that impede the normal performance of their tasks.

Besides the risks arising from crisis situations, general risks arising from the CA's inspection activities should be analysed and strategies to prevent or mitigate the risks should be

implemented. One strategy for managing risks is to create a 'risk register', which is subject to regular review to ensure that the risks identified remain relevant and that the controls in place to prevent or mitigate the risks are sufficient (Table 1).

Examples of risks arising from the activities of an inspectorate:

- Lack of expertise in the conduct of an inspection;
- Failure to anticipate the impact of a new regulation;
- Insufficient resources to ensure that inspections are carried out in an appropriate manner;
- Failure to identify non-compliances or malpractice during an inspection (e.g. due to the establishment temporarily or intentionally ceasing one or more activity);
- Lack of consistency by inspectors in applying the regulation, national legislation, or standards;
- Relevant observations highlighted by an inspector in their inspection notes during an inspection are not included in the inspection report;
- A complaint by an establishment on the decisions taken by the inspectorate or the lack of fair treatment by an inspector;
- Unreasonable delay in taking enforcement action;
- Loss or improper release of confidential data;
- Inadequate training, qualification and/or development of inspectors.

Table 1: Example of a Risk Register.

Risk	Causes	Effects	Mitigating Factors	Additional Actions Taken
• Inconsistency of inspectors in applying legislation, regulations or standards.	• Insufficient training of inspectors • Inadequate guidance/ • Procedures for inspectors to follow.	• Loss of stakeholder confidence. • Increased risk of challenges to regulatory decisions. • Risk to public health.	• Quality assurance of inspection reports. • Mentoring new inspectors. • Continuous training and development.	• Audit of inspection reports. • Audit of Inspection Evidence Forms. • Review of training programme.

2.2.7 Procedures for taking urgent measures for the protection of public health

Procedures should be in place for taking urgent measures necessary for the protection of public health. As a minimum, procedures should be in place for:

- Investigating a suspected quality defect of a SOHO preparation (*e.g.* a procedure conducting independent quality control tests), (if applicable);
- Investigating serious adverse events and reactions;
- Taking action during an inspection e.g. quarantining defective SOHO or SOHO preparations, (if applicable);
- SOHO preparations recall, (if applicable);
- Immediate revocation/suspension of a licence;
- Rapid alert from national to European /third country level;
- Communication with the media and external stakeholders, (if applicable);
- The procedures should include a decision-making process to ensure that the balance of risks between protecting public health and the benefits of ensuring a continued supply of the product is fully considered.

2.2.8 Procedures for identifying illegal and fraudulent activity (IFA)

The management in the EU of suspected IFA relating to SoHO is diverse and lacks harmonisation. These Guidelines recommend that CAs include procedures in the quality management system relating to the identification and management of IFA. A detailed guide on investigating IFA was developed as part of the SoHO Vigilance and Surveillance Project[2].

The IFA guide contains comprehensive tools and a list of SOPs covering all stages of an investigation into illegal and fraudulent activity.

2.2.9 Exchange of information between EU Member States/Competent Authorities

Information and data may be exchanged on a confidential basis between SoHO competent authorities and between SoHO national authorities and the Commission, and shall not be disclosed without the prior agreement of the SoHO competent authorities from whom that information originates.

The EU SoHO Platform shall provide a secure channel for restricted exchange of information and data between SoHO entities, SoHO competent authorities, MSs and the Commission concerning SoHO and SoHO activities.

On the EU SoHO platform, the following information shall be made publicly available by CAs:

- A register of registered SOHO entities;
- A register of SoHO establishments authorised by the CA;

[2] The detection and investigation of suspected illegal and/or fraudulent activity (IFA) related to tissues and cells - Report and Guidance. Deliverable 7 of the SoHO V&S project of 25 june 2011

- Authorised SoHO preparations;
- Approved SoHO clinical studies;
- Relevant best practices documented and published by the SCB;
- Technical guidelines published by ECDC and EDQM;
- Quality management guidelines published by EDQM;
- More stringent measures the MS has adopted than those provided for in the Regulation;
- Annual report of SoHO establishment activities;
- Annual summary of confirmed SAR or SAE notifications and of the related investigation reports;
- SoHO compendium;
- The list of the existing substances, products or activities for which an opinion on the regulatory status under this Regulation is not available and is needed;
- The name, the institution of origin and the declaration of interests of each SCB member and alternate;
- The list of SoHO national authorities;
- The rules of procedure of the SCB, the agenda and the summary minutes of each meeting, unless such publication undermines the protection of a public or private interest.

The EU platform shall also be used to communicate the following information:

- Where a CA is in receipt of an SAR or SAE notification or other information with implications for quality, safety or supply of SoHO in more than one MS;
- Supply alerts received by the CA where the supply interruption might affect other MSs and where such interruption might be addressed through cooperation, including through exchange of SoHO, between MSs;
- MSs allowing for the compensation of SoHO donors. The conditions for compensation shall be made available to the SCB for sharing with other CAs on the EU platform.
- Where SoHO CAs have delegated SoHO supervisory activities to delegated bodies, the names and contact details of the delegated bodies, as well as details of the delegated supervisory activities shall be submitted to the SoHO platform.
- Where any decision to permit the distribution, or preparation for immediate human application, of SoHO preparations, even if not all procedures regarding preparation authorisation have been carried out, this information shall be communicated to the Commission and other MSs through the EU platform.

CAs must ensure that any release of information is compatible with national legislation.

2.2.10 Exchange of information with other regulatory authorities or third countries

Where relevant, CAs should have in place procedures for exchanging information with other national regulatory authorities which regulate activities that may impact upon the quality and safety of SoHO. For example, if the CAs responsible for regulating medical devices and/ or medicines or gametes are separate from the CAs for other SOHO, there should be an information

sharing agreement in place that ensures that there is effective communication flow. The agreement should ensure that where a serious non-compliance is identified by another regulatory authority that has the potential to impact on the safety of SoHO the relevant information is communicated swiftly and without undue delay.

MSs may exchange confidential information with regulatory authorities of third countries with which they have concluded bilateral or multilateral confidentiality arrangements, as necessary and proportionate for the protection of human health (article 75.4).

2.2.11 Management of complaints

CAs should establish and maintain a procedure for documenting and managing complaints, relating to the activities of its inspectorate, personnel, and any contracted persons or organisations. This procedure should include the rights to appeal inspectorates' decision. Records of the complaints and appeal received, and the actions taken should be retained in accordance with the records' retention policy.

2.2.12 Management of conflicts of interest

SoHO competent authorities shall ensure that personnel performing SoHO supervisory activities, including inspectors, assessors, and vigilance officers have no financial or other interest that might be considered prejudicial to their independence and that they are not placed in a situation that may, directly or indirectly, affect the impartiality of their professional conduct.

Personnel performing SoHO supervisory activities shall provide a declaration of their interests and regularly update that declaration. On that basis, SoHO competent authorities shall take the relevant measures to mitigate the risk of conflict of interests. CAs should have a clearly defined policy for the management of conflicts of interest. The policy may include a provision that inspectors may not inspect a SoHO establishment for a defined number of years after having previously been employed at the establishment.

Effective management of conflicts of interest is important because if they are not identified and controlled, they can undermine the integrity of the decisions and the actions taken by a CA.

When an inspector is identified as compromised by a conflict of interest, the other inspections carried out by them should be retrospectively assessed to ensure that they were not similarly compromised. There should be a procedure that describes how to review, modify or cancel an official decision if it is proven that an inspection or a decision-making process was compromised by a conflict of interest or inappropriate/corrupt conduct by a member of staff.

2.2.13 Delegation of SoHO supervisory activities to other bodies

MSs may empower a SoHO competent authority responsible for certain SoHO supervisory activities to delegate that SoHO supervisory activity to one or more other bodies (‘delegated bodies’).

SoHO competent authorities that delegate SoHO supervisory activities to a delegated body shall have in place a written agreement with that delegated body. The provisions to be included in the written agreement are detailed in Article 9(3) of Regulation (EU) 2024/1938.The SoHO competent authority shall regularly conduct audits of the delegated bodies. Even when SoHO supervisory activities are delegated, the CA remains legally responsible for ensuring compliance with the Regulation.

3 SoHO Entities, SoHO Establishments, Importing SoHO Establishments and SoHO Preparation Authorisation

References

- Register of SoHO entities (art. 16).
- Registration of SoHO entities (art. 17).
- SoHO preparation authorisation system (art. 18).
- Authorisation of SoHO preparations (art. 19).
- SoHO establishment authorisation system (art. 24).
- Authorisation of SoHO establishments (art. 25).
- Authorisation of importing SoHO establishments (art. 26).
- Application for SoHO establishment authorisation (art. 46).
- Application for importing SoHO establishment authorisation (art. 48).
- Significant changes (Implementing Act on Import, not yet adopted).

3.1 Introduction

Regulation (EU) 2024/1938 details the requirements for CAs to maintain oversight of SoHO activities. This includes the requirement for SoHO entity registration, SoHO establishment authorisation, importing SoHO establishment authorisation and SoHO preparation authorisation. Competent Authorities shall have in place systems and processes that ensure that the implementation requirements of the Regulation (EU) 2024/1938 are met with regards to these registrations and authorisations. Systems and processes should enable a CA to make evidence based decisions in relation to registration, and the granting or refusal of an authorisation.

3.2 SoHO Entities

CAs shall have procedures in place for the registration of SoHO entities. Registration can be through national registries or the EU SoHO Platform. Information on the process and requirements for registering as an entity should be clearly explained on CAs' websites. The CA should provide detailed procedures on the maintenance of the register and verification of the information provided by the entity. There should be clear instructions on what supporting documentation is required for the verification process.

The CA is responsible for the verification of information supplied by the entity. If a national registry is used, the CA shall ensure that this information is submitted onward to the EU SoHO platform.

The transfer of data from the national registry to the SoHO platform should be clearly described. The guideline and templates for registration of entities from the SCB can assist the CA in developing their processes.

The register shall include reference to the entities registered, authorisations required by the entity (SoHO establishment authorisation, importing SoHO establishment authorisation, SoHO preparation authorisation) as well as the identification of critical entities. This information can assist CAs with inspection planning.

SoHO competent authorities shall be responsible for ensuring that the information regarding the SoHO entities on their territory registered pursuant to Article 17 in the register of SoHO entities and on the EU SoHO Platform is consistent and shall submit any changes in that information to the EU SoHO Platform without undue delay.

CAs shall ensure that procedures are in place for the necessary European coding system as per the SoHO Regulation, i.e. Single European Code (SEC). CAs shall ensure that such identification complies with the technical standards established for that coding system. For that purpose, CAs may use a SoHO establishment identification code generated by the EU SoHO Platform.

Further information on the registration process for entities and use of SoHO platform is provided by the SCB.

3.3 SoHO Establishment Authorisation

A SoHO entity that carries out any of the following SoHO activities requires a SoHO establishment authorisation before any SoHO activities take place:

- Both processing and storage;
- Release;
- Import;
- Export.

Entities performing importation require a specific importing SoHO establishment authorisation, which is discussed under section 3.3.2.

3.3.1 SoHO Establishment Authorisation application procedure

SoHO CAs shall ensure that there is a system in place for the application and assessment of establishment authorisation applications. This system shall take into account relevant guidelines and templates from the SCB. Information on the process and requirements for applying for an authorisation should be clearly explained on CAs' websites. The information provided should include guidance on the regulations, national legislation and standards that must be complied with for each of the activities to be authorised. Provision of accessible and clear information will

help applicants to prepare thoroughly before submitting an authorisation application, reduce the number of unsuitable authorisation applications submitted, and the resources required to manage them.

New sites should have access to sufficient information to enable them to understand responsibilities and carry out their role effectively and in accordance with EU and national legislation.

The authorisation application process should be designed to provide a CA with sufficient information to make a preliminary assessment of an establishment's suitability to be authorised. To facilitate harmonisation and mutual recognition, CAs should use the document 'Proposed format for SoHO Establishment Dossier (SED)' for collection of information from SoHO establishments. This will assist with an authorisation application and, for on-going authorisation management. In the case of CAs which already have in place an authorisation application form, they should ensure that (as a minimum) all the information required in the SED is captured within the existing authorisation application form.

CAs may use the secure communication channel on the EU SoHO Platform for the exchange of documents relating to the application for a SoHO establishment authorisation, with the SoHO establishment. Guidelines for the use of the EU SoHO platform should be followed at all times and incorporated within CA guidelines as necessary.

The application should include any agreements between the applicant and any entities which will provide contracted activities. The roles and responsibilities of each party should be suitably detailed. Additional supporting information may be required by the CA, such as, suitability of premises, site plans, information on quality system, specific SOPs, overview of system in place for retention of traceability documents, contingency and emergency plans.

Following submission of a completed application, the CA shall acknowledge receipt of application, assess the application, carry out an onsite inspection of the SoHO establishment (and where applicable of contracted SoHO entities and/or third parties). Based on the outcome of the application assessment and relevant inspection(s), a decision to grant an authorisation or refuse an authorisation should be made, with the outcome communicated to the applicant. Timelines to make such decisions should be in place.

There should be a documented process that describes how the information provided in an authorisation application and if applicable, the evidence reviewed during the onsite inspection, should be evaluated to support a decision whether:

- To grant an authorisation, with/without restrictions;
- To refuse an authorisation application.

CAs should establish clear and accessible policies outlining the procedures for appealing decisions pertaining to authorisation applications, whether the application is rejected or granted with restrictions.

In instances of incomplete applications, a structured process must be in place for requesting any missing or incomplete information. This process should specify clear timelines for the submission of additional information. Should the applicant fail to provide satisfactory

information within these defined timeframes, the application should be rejected, and the applicant encouraged to submit a new application.

3.3.2 Authorisation of Importing SoHO Establishments

An authorisation is also required for the importation of SoHO into the EU. Importation shall not occur within a SoHO entity or SoHO establishment without them being authorised as an importing SoHO establishment. National and international registries organising import of SoHO should also be authorised as importing SoHO establishments.

CAs shall ensure that a system is in place for the receipt and assessment of importing SoHO establishment applications. This may include any requirement to inspect third country suppliers and shall ensure that procedures are in place at the requesting importing SoHO establishment to make sure that the imported SoHO are equivalent in terms of quality, safety and effectiveness to the SoHO preparations authorised in accordance with the SoHO Regulation and in accordance with any SCB guidance. The importing SoHO establishment shall be responsible for the physical reception and visual examination and verification of imported SoHO prior to their release. This involves verifying coherence between the received SoHO and the associated documentation and assessing the integrity of packaging, labelling, and transport conditions. The releasing officer shall release imported SoHO for distribution only after confirming compliance with the applicable standards and satisfactory completion of physical and documentation checks.

When the import of SoHO is organised for a specific SoHO recipient, an authorised importing SoHO establishment can delegate the responsibilities of physical reception, visual inspection, and verification to the SoHO entity applying the SoHO.

CA's should assess whether the requirements of the application have been met regarding documents that must be provided. The Implementing act on import specifies the information to be provided in an application for an importing SoHO establishment authorisation. CAs should use the document 'Proposed format for SoHO Importing Establishment Dossier (SIED)' for collection of information from SoHO establishments. The annex to the Inspection Guidelines titled 'Import/Export' covers the inspection of Importing SoHO Establishments.

3.3.3 Changes to SoHO Establishment Authorisation

CAs should have in place documented procedures for renewing (if applicable) and amending establishment authorisations. The procedures should also allow for the suspension or withdrawal of SoHO establishment authorisations.

3.3.3.1 Significant changes to SoHO Establishment Authorisation

SoHO establishments shall not make any significant changes regarding the SoHO or SoHO activities for which they have been authorised, without prior written authorisation from the CA. CAs shall have in place procedures for the management, evaluation and authorisation or rejection of significant changes. This should also include any SoHO establishment authorisation updates that may be required. Any procedure should include the consideration whether an inspection is required for the change and how to document the decision to accept or refuse the proposed change. A significant change to a SoHO preparation authorisation may require a change to the SoHO establishment authorisation. Procedures in place should consider this potential interaction. Changes to a SoHO preparation authorisation may require updates to the SoHO establishment authorisation. Procedures should address this interaction and also assess whether changes to the preparation process authorisation are needed. Relevant guidance on preparation process authorisation should be incorporated into any authorisation processes.

Significant changes shall include:

- Changes to types of SoHO concerned for example: initiation of a new SoHO or a new SoHO preparation at an establishment;
- Changes to types of SoHO activities carried out (*e.g.* donor history review, processing, release);
- The use of new premises or modification of premises which may impact the conditions under which SoHO activities are carried out (*e.g.* change to air handling systems; change to storage area);
- Changes of administrative nature, related to the SoHO establishment authorisation, including a permanent or temporary replacement of the responsible person.

The following can be considered as examples of other significant changes:

- Change in equipment which may impact SoHO activities (*e.g.* introduction of new equipment for an authorised process, or a change to IT system which impacts on the quality and safety of SoHO);
- Cessation of a SoHO activity (*e.g.* no longer supplying a specific SoHO);
- Change in SoHO entity performing SoHO activities on behalf of SoHO establishment (*e.g.* new entity performing SoHO collection, donor testing);
- Other changes in the preparation process of a SoHO (see SCB guidance on this).

Some significant changes require an update of the PPD or the SED or both. In these cases, the relevant processes and guidelines issued by the SCB should be followed

3.3.3.2 Significant changes to Importing SoHO Establishment Authorisation

Importing SoHO establishments shall seek prior written approval of the CA for any significant changes to their importing activities. Significant changes that require prior written authorisation

are formulated in the Implementing Act on Import (article 3). CAs should consider implementing procedures for the management, evaluation and authorisation or rejection of significant changes. This should also include any SoHO importing establishment authorisation updates that may be required. Any procedure should include whether an inspection is required for the change and how to document the decision to accept or refuse the proposed change.

Some significant changes require an update of the PPD or the SIED or both. In these cases, the relevant processes should be followed.

3.3.3.3 Administrative changes to an Authorised SoHO Establishment

SoHO establishments can register administrative changes on the SoHO platform without prior approval of the CA, such as change in correspondence details or a change in company/establishment name (without a change in legal entity).

3.3.4 Suspension or Withdrawal of SoHO Establishment Authorisation

CAs may suspend the authorisation of a SoHO establishment, or specific activities within the establishment's authorisation.

This can be done where SoHO supervisory activities (*e.g.* inspection or serious adverse reactions or events) demonstrate or give reasonable concerns that the SoHO establishment does not comply with the conditions of its authorisation or with the SoHO Regulation. This can also be done if there is an imminent risk to the safety of SoHO donors, recipients or offspring from medically assisted reproduction or an imminent risk of unnecessary wastage of critical SoHO (for instance in certain situations when blood is distributed but not used without good reasons).

Withdrawal can be considered by the CA where SoHO establishments are unable to rectify non-compliances after multiple warnings, or after a suspension of authorisation, within an agreed timeline. This may also be done in cases where a suspension is not considered sufficient to address the issues identified. Withdrawal may also be considered in circumstances where a SoHO establishment has had their authorisation suspended repeatedly.

CAs shall have a system in place to allow for the suspension or withdrawal of SoHO establishment authorisations. This should consider actions to be taken by CA and establishment and the process for ongoing review of the situation and reimplementation of authorisation, if applicable. This process shall ensure that any change to the authorisation status is updated on the EU SoHO Platform without undue delay.

3.4 SoHO Preparation Authorisation

A SoHO entity must obtain approval from a Competent Authority through a SoHO preparation authorisation under the following circumstances:

The SoHO:

- Is subjected to processing (and where relevant one or more other SoHO activities as defined in the SoHO Regulation);
- Has a specific clinical indication; and
- Is intended for human application to a SoHO recipient or is intended for distribution.

SoHO entities shall not release, or for autologous or within relationship use, shall not prepare and immediately apply to a SoHO recipient a SoHO without prior SoHO preparation authorisation.

CAs shall provide guidelines and templates for the submission of applications for SoHO preparation authorisations. CAs shall take into account the templates and guidance published by the SCB in relation to the application process and assessment of preparation authorisations. The application process and assessment shall include a benefit risk assessment which will provide information on the further evidence required to ensure safety and effectiveness of the SoHO. e.g. clinical outcome monitoring.

Assessment of applications shall be performed by SoHO assessors, with communication between assessors and inspectors as necessary. CAs shall conduct the assessment of applications through remote document review or onsite inspection. The inspection process can be used to confirm information submitted with the application is appropriately applied onsite.

If an application for SoHO preparation authorisation has already been authorised in another SoHO entity, in the same or other MS, then the authorisation procedure may be simplified provided the CA receiving the application has verified with the permission of the SoHO entities concerned, that the SoHO activities performed and the steps of the processing applied for the already authorised SoHO preparation are carried out by the applicant SoHO entity in such a manner that the quality, safety and effectiveness results of the SoHO preparation will be equivalent to those demonstrated in the SoHO entity where the SoHO preparation was first authorised. Details on this process and assessment should be available, taking into account any templates and guidance from the SCB.

Where requested SoHO preparation assessors may carry out joint assessments of SoHO preparations with other MS CAs.

The requirement for a SoHO preparation authorisation shall be waived for SoHO intended to be distributed for the manufacture of products regulated by other Union legislation. A derogation may also be granted in health emergency situations. CAs should have a process in place for dealing with health emergency situations and any derogations granted / no objection issued.

4 Inspection

References

- General responsibilities and obligations of SoHO competent authorities (art. 8).
- Inspections may be performed as part of the SoHO preparation assessment (art. 20.6).
- Authorisation and Inspections of SoHO establishments (art. 25 and art. 27).
- Inspection may be performed to SoHO entities or third parties contracted by the SoHO establishment, within the context of a SoHO establishment inspection (art. 25.2 and 45.2).
- Authorisation of importing SoHO establishments (art. 26).
- Inspections of SoHO entities, other than SoHO establishments, and third parties (art. 28).
- Joint inspections (art. 29).
- Inspections may be performed in the context of SAR or SAE notifications (art. 33.6).
- SoHO establishments shall not carry out any activities without prior authorisation (art. 45.1).

'*Inspection*' means a formal and objective control by a SoHO competent authority or delegated body to assess compliance with the requirements of the SoHO Regulation and other relevant Union or national legislation.

CAs shall carry out inspections of SoHO establishments within their MS, and also SoHO entities, third country suppliers or contracted third parties, when applicable (for guidance on this see "*Risk-Based Inspection of SoHO Entities, Third Parties, and Third Country Suppliers*"). CAs may also participate in joint inspections. Inspections shall be carried out against the SoHO Regulation and its implementing acts, national legislation and the most recent technical guidelines published by the ECDC and EDQM.

This chapter describes the different inspection methods (onsite, virtual/remote, joint inspection), different types of inspection (routine, non-routine and follow-up) and the different activities to inspect. It additionally outlines the procedures for conducting an inspection, along with all related aspects.

For some topics, further guidance has been developed for inspectors on what to take into account when performing an inspection of a SoHO entity:

- '*Inspection of Medically Assisted Reproduction (MAR) establishments*' describes the specifics when inspecting MAR;
- '*Inspection of medical devices and in vitro diagnostic medical devices in SoHO entities*' describes what SoHO inspectors could look at when they come across medical devices and in vitro medical devices in SoHO entities;

- '*Inspection of computerised systems in SoHO entities*' describes what inspectors can look at when inspecting computerised systems in SoHO entities;
- '*SoHO vigilance for inspections*' describes inspection of vigilance and traceability systems.

Inspections of SoHO entities can be carried out as:

- Announced routine systems inspection;
- Follow-up inspections;
- Inspections in response to receipt of an SoHO establishment authorisation application or notification of significant change in activities;
- Inspections in response to a SOHO Assessor request, following receipt of a SoHO preparation authorisation application or notification of significant changes;
- Announced or unannounced inspections - for investigation of fraudulent or other illegal activity;
- Announced or unannounced inspections targeting a specific activity or topic e.g. related to an SARE.

Inspections of SoHO entities shall be carried out through onsite inspections or exceptionally through virtual means or remote document review.

Virtual inspections or remote document review can only be considered when:

- Such inspection methods do not pose a risk to the quality and safety of SoHO;
- Such inspection methods do not prejudice the effectiveness of inspections;
- Protection of SoHO donors, SoHO recipients or offspring from medically assisted reproduction is respected; and
- The maximum interval between two onsite inspections at a SoHO establishment shall not exceed 4 years.

When SoHO entities choose to use guidelines other than those referred to in the SoHO Regulation, the inspectors shall evaluate the steps taken by the SoHO entity to ensure the adequacy of the guidelines or technical methods and their compliance with the standards set out in the Regulation. Harmonised guidelines for inspectors assessing technical requirements defined in the EDQM/ECDC guidelines will be published by the SCB.

4.1 The role of the inspector

For the purposes of these Guidelines the primary role of an inspector is to verify that SoHO entities (including SoHO establishments, importing establishments and entities or third parties, when relevant), are compliant with EU and national legislation and applicable guidelines and to initiate appropriate action when non-compliances are identified. Inspectors should work in cooperation with SoHO preparation assessors when applicable.

Inspectors should understand the limits associated with conducting inspections and their role and powers should be clearly documented within legislation and the CA QMS. It should be made

clear to inspectors (and entities) that an inspection is a sampling exercise as inspectors cannot examine all areas of each activity subject to inspection and associated documentation during an inspection. Similarly, an inspector is not responsible for non-compliances that could not be observed during the inspection due to limited time or scope or because certain processes could not be observed during the inspection.

During an inspection, inspectors should provide clear instruction to the entity about what the Regulation, national legislation, and guidelines require in order to demonstrate compliance.

Inspectors should avoid:

- Providing recommendations regarding specific equipment types;
- Recommending any specific service provider;
- Becoming the SoHO entity consultant.

4.2 Inspection Methods

4.2.1 Onsite Inspection

Onsite inspection requires the physical presence of the inspection team at the site being inspected. This enables the direct review and examination of documentation, facilities, equipment, SoHO and activities. This allows for the inspection to cover multiple processes and activities for a routine system inspection; to perform an initial assessment of an entity's activities; review specific evidence in relation to fraudulent or other illegal activity; or to review details of a specific SARE.

The interval between two onsite inspections at a SoHO establishment shall not exceed four years. This time period and previous inspection methods should be considered when planning inspections, using the specific SoHO establishment risk assessment tool.

An onsite inspection is required when an application for a SoHO establishment authorisation is received by the CA and may be required as part of the assessment of a SoHO preparation authorisation application.

4.2.2 Virtual Inspection and Remote document review

Virtual inspection is the conduction of an inspection without the inspector(s) being physically onsite, this can be done through various IT applications. A remote document review, is the review of relevant documents without the inspector being physically onsite and this can be done offline or through information sharing platforms. Remote document review can be performed as part of a virtual inspection, or can be a standalone control measure.

CAs may implement a process for virtual inspections or remote document review in specific situations, between the onsite inspections. This can be in part (with some aspects addressed onsite), or in full.

Virtual inspection/remote document review (in part or in full) shall only be carried out if:

- Such inspection modes do not pose a risk to the quality and safety of SoHO;
- Such inspection modes do not prejudice the effectiveness of inspections;
- Protection of SoHO donors, SoHO recipients, or offspring from MAR is respected; and
- The maximum interval between two on-site inspections (four years) at a SoHO establishment, is not exceeded.

Additional consideration should be given to the following when considering a virtual inspection:

- The SoHO entity has already been previously inspected and declared compliant with National /EU requirements;
- The most previous inspection did not indicate any critical or major non compliances;
- Absence of notification of major SAREs, unless the conclusion of the investigation doesn't exclude the necessity of an onsite inspection.

Virtual inspection/remote document review may be indicated in the following circumstances:

- To review activities in advance of an onsite inspection;
- To evaluate changes to an entity's activities (when virtual inspection or remote document review is considered appropriate);
- As an intermediate evaluation between two onsite general systems inspections;
- Where imported SoHO are not physically received by the importing SoHO establishment but sent directly to the SoHO entity for human application (*e.g.* stem cell registry) or to an operator for manufacturing a product which is regulated by other Union legislation (e.g. ATMP manufactures).

The communications platform for a virtual inspection should be agreed in advance of the inspection. Virtual inspections may require the sharing of electronic copies of documents with the inspector, live sharing of documents, videos, or screen sharing for demonstration of activities. The CA may have their own suitable communication for the virtual inspection or may request that the entity proposes a suitable platform. If applicable, consideration can be given to the need for a virtual review of physical facilities, equipment or processes and if and how this can be managed virtually *i.e.* live streaming from site, virtual reality, etc. Reliable internet access and equipment (*e.g.* laptops, monitors, cameras) for inspectors and sites should be considered as an essential part of virtual inspection.

Any method of virtual inspection or remote document review should ensure the confidentiality of the information being shared

4.2.3 Joint Inspections

Joint inspections may be requested:

- Where an entity performs SoHO activities in more than one MS;
- Where specialist technical expertise is required;
- If other reasonable grounds indicate a joint inspection could be carried out *e.g.* to investigate information related to a SARE or fraudulent or illegal activity.

Joint inspection could also be considered for the following situations:

- Inspection of entities/third country suppliers who supply to more than one MS;
- To assist in the training of inspectors or expansion of inspector knowledge of smaller MS;
- Alert/urgent situation affecting more than one MS or taking place in MS where adequate inspectors are unavailable in a particular moment of need or needing extensive human resources;
- When there are insufficient numbers of inspectors in a MS to meet the requirements of performing onsite inspections of SoHO establishments every 4 years. A guest inspector from another MS may be added to the inspection team to meet this requirement period.

EU joint inspections will help to ensure that inspectorates across the EU are taking a consistent approach to the practical interpretation of the SoHO Regulation, the consistency of the inspection methodology, the classification of non-compliances and follow-up procedures for non-compliances. The conduction of joint inspections may also be used as a tool for inspectors to transfer the experiences gained during these inspections to their national CA. In general, SoHO competent authorities shall make all reasonable efforts to ensure that inspectors participating in requested joint inspections have completed the relevant Union training as per the SoHO Regulation.

The code of practice published on the SoHO platform should be used to draft the CA process for joint inspections. This document aims to establish a framework for joint inspections by multi-MS teams and to provide assistance to the CA inspections function in organisation and performance of joint inspections.

4.3 Inspection types

4.3.1 Routine inspections

A routine inspection is one that is scheduled in advance as part of the regular inspection cycle within a CA to ensure compliance to the Regulation is maintained.

Implementation of a risk-based inspection programme will enable a CA to make evidence- based decisions as to the frequency, type and method of routine inspection that ought to be scheduled for an establishment taking into consideration the activities undertaken and the level of risk attributed to the establishment, including the criticality of supply. The documents '*Risk-based inspection planning of SOHO Establishments'* and 'Risk-based inspection planning of SoHO entities, third parties and third country suppliers' can be used as guidance.

The routine inspection process should be used for general systems inspections or for other inspection types identified through the risk-based inspection scheduling, such as thematic

inspections. Conducting a thematic inspection provides an opportunity for inspectors to conduct an in-depth inspection focusing on one or two areas of activity and to identify areas for improvement that may not be picked up during a general systems inspection.

It is recommended that a general systems inspection is carried out before an establishment is authorised, as per CA procedures, and the yearly interval for onsite routine inspections should be determined through risk assessment (with the interval between two onsite inspections not exceeding four years).

A routine inspection is preferably conducted by a team of at least two inspectors. The evidence that should be reviewed for each type of inspection is set out in the document '*Inspection process*'.

4.3.2 Non-routine inspections (for cause)

Although a CA will have an inspection scheduling programme in place, there may be occasions where inspections are required to be performed outside of this schedule. These non-routine inspections may arise when inspections are required to focus on specific concerns.

A non-routine announced inspection may be scheduled:

- In response to a serious adverse event or serious adverse reaction in a donor or recipient;
- In response to a reported significant change to the activities or SoHO authorised;
- On request of an assessor regarding a request for a SoHO Preparation Authorisation;
- To investigate specific issues following a request from a CA in another Member State or other official authority.

A non-routine unannounced inspection may be scheduled (as per CA procedures), to:

- investigate a suspicion of illegal or fraudulent activity;
- investigate serious breaches of legal requirements which might expose donors or recipients to risk;
- investigate a serious adverse reaction resulting in a patient death or a major product recall.

These inspections may take place at short notice. The CA shall consider all relevant information in advance of the inspection and decide if the inspection should be announced or unannounced, and if the inspection is required onsite or if any aspect can be carried out through remote document review or other virtual methods. Generally, inspections for fraudulent and illegal activity should be performed via an unannounced inspection.

It is essential for a CA inspection function to have sufficient capacity and authority to conduct non-routine inspections quickly and effectively.

The CA should have a process in place for these non-routine inspections which considers the reason for inspection and any other available information or known risks at the site and determine if notification of inspection is required and if any additional personnel are required, such as enforcement officers or police or other authorities. Performance of an onsite inspection or

remote document review can also be considered. An onsite inspection should be carried out if there is a risk or potential risk to SoHO donor, SoHO or patient safety.

Remote document review may be considered if applicable. For example, where imported SoHO are not physically received by the importing SoHO establishment but sent directly to the SoHO entity for human application or to an operator for manufacturing a product which is regulated by other Union legislation (*e.g.* ATMP manufactures). These inspections may require focus on a process/SOHO preparation which may follow part of the donor to recipient chain *i.e.* the chain from the donor to the distribution of the SoHO.

The inspection should be performed by a minimum of one inspector and preferably at least two, unless the inspector is also an assessor or a technical expert in the process steps concerned. Solo inspections should be avoided where possible. One or more additional experts in a field relevant to the process under consideration may also be required.

4.3.3 Follow-up inspections

A follow-up inspection may be required to assess whether corrective actions put in place to address non-compliances identified during a previous inspection have been properly implemented and that they are achieving the intended outcomes.

4.4 Activities to inspect (as applicable to each site)

The specific SoHO activities which an entity has registered or where a SoHO establishment is authorised will be inspected during a routine inspection (with an onsite inspection at least every four years for a SoHO establishment). It is important to review a wide range (if not all) of SoHO activities during the routine inspection. Inspection of these SoHO activities may also be required during designated thematic inspections; or for review of a specific topic.

Based on the type of inspection, the CA shall determine if an onsite inspection is required. Onsite inspections would be beneficial for inspection of specific activities as this would provide an opportunity for an in-depth inspection and an opportunity to identify areas for improvement that may not be picked up/identified during a general systems inspection. The aim of this section is to provide information on the specific SoHO activities which can be reviewed on any type of inspection, including at entities. The document titled *'Inspection process'* can be used to determine what inspection evidence is required. The sections below can assist with some relevant areas to review. Harmonised guidelines for assessing technical requirements defined in the EDQM/ECDC guidelines and which have become mandatory in inspections will be published and should be utilised.

4.4.1 General inspection focus

Inspectors shall assess whether the entity complies with the standards set out in the SoHO Regulation and any additional National Legislation. In cases where the SoHO entities follow the technical guidelines published by the ECDC and by the EDQM, the inspectors shall consider the standards set out in the Regulation to be met, insofar as they are addressed by such guidelines. If the entity follows other guidelines, they need to be adopted by the MS. If other guidelines or technical methods are followed, the inspectors shall evaluate the steps taken by the SoHO entity to ensure the adequacy of such guidelines or technical methods, and their compliance with the standards set out in the Regulation).

The general inspection focus should be on:

- Verification of the validity of SoHO entity's registration or SoHO establishment authorisation status, including the authorisation status of all SoHO preparations and their listing on the EU SoHO platform. This can be performed in advance on inspection.
- Confirmation that all regulated SoHO activities are accurately documented and traceable.
- Assurance that a qualified Responsible Person, and where applicable, a Releasing Officer and Medical Doctor, are appointed.
- Verification of staff training, qualification, and competence for all critical tasks.
- Confirmation that records of staff training, qualifications, and competence assessments are current and tailored to specific roles.
- Verification that a documented Quality Management System (QMS) is implemented, up-to-date, and regularly reviewed.
- Examination of non-conformances, recalls and complaints.
- Examination of the availability of internal audits, deviation logs, and management review reports, along with the implementation of resulting actions.
- Examination of the change control system.
- Assurance that Corrective and Preventive Actions (CAPA) procedures are consistently applied and their effectiveness verified.
- Verification of the use of quality risk management.
- Review of documentation demonstrating that the QMS encompasses all authorised SoHO activities, including import/export when applicable.
- Assurance that all Serious Adverse Events and Reactions (SAE/SAR) are identified, documented, investigated and reported within required timelines.
- Verification of donor eligibility requirements.
- Examination of quality control systems.

- Verification of the presence and functionality of a validated traceability system covering donors, recipients, and offspring.
- Review of traceability and follow-up documentation linking donor, recipient, and offspring.
- Assurance that traceability encompasses all critical materials, reagents, and devices used in SoHO activities, confirming that donor-recipient-offspring identifiers are unique, secure, and confidential.
- Premises - located, constructed, adapted and maintained to suit the activities to be carried out.
- Equipment qualification, calibration and maintenance.
- Validation of systems, process and tests.
- Examination of contract management system.
- Review of compliance with data-protection legislation and adherence to data-retention timelines.

Note: Previous SARE notifications should be considered when deciding on specific inspection activities.

4.4.2 SoHO Donor registration

SoHO donor registries shall require registration as a SoHO entity.

SoHO donor registries can be used to record details of SoHO donors, SoHO donated, and information needed to identify a match with a potential SoHO recipient. These registries can be used to transfer information to other registries where appropriate. These registries can be national or international and must be registered as a SoHO entity in the country in which they are located.

Inspection of a specific SoHO donor registry may be warranted under the following conditions:

- To assess the registry's processes and evaluate how quality and safety standards, as outlined in the SoHO Regulation, have been verified.
- If there are any concerns regarding the safety of SoHO donors, recipients, or offspring.

Registries which organise the import of SoHO should be authorised as an importing SoHO establishment. The imported SoHO may be received directly at the SoHO application centre. There should be an appropriate system in place detailing the activities of the registry and the tasks delegated to the SoHO application centres, such as physical checking of imported SoHO and associated documentation and applying the SoHO to the SoHO recipient. The process for reporting suspected adverse reactions or events should be appropriately detailed. Release can be completed remotely by the importing SoHO establishment.

Follow up requirements of donors and recipients should be detailed and should reflect any guidance available such as from professional bodies (*e.g.* ESHRE; EBMT; ECCTR; EATCB).

If SoHO can be donated repeatedly, there should be a process in place to verify that the donor is not donating more frequently than what is outlined as safe within the appropriate technical guidelines. Registration of SoHO donors can be through the SoHO entity's registry or national or international registries and these can be used to verify frequency of donation. The suitability of the SoHO donor registry used should consider the interconnectivity of SoHO donor registries and the ability to verify donation frequency and mitigate risks to the donor.

An inspection at an entity which performs donor registration may be considered if the donor registry facilitates the provision of SoHO to multiple MSs.

An inspection may also be considered to check that no advertising or promotional materials refer to compensation;

A registry which is authorised as an importing SoHO establishment should undergo routine inspection. Verification of any tasks delegated to the SoHO application centres may be indirectly performed through the auditing of the SoHO application centres by the registry *i.e.* physical and documentation checks in relation to the SoHO received.

4.4.3 SoHO Donor history review and medical examination/assessment

SoHO donor history review and medical examination/assessment, is an important step in protection of donors and recipients, as well as offspring from MAR. It should be verified that these activities are carried out under conditions that protect the health of the SoHO donor and SoHO recipient. Records in relation to these activities should be maintained according to the SoHO Regulation and relevant national law and made available for inspection. A physician should be appointed who is responsible for tasks such as development, review and approval of procedures for establishing and applying SoHO donor eligibility criteria and procedures for SoHO collection (article 50).

Verification of any tasks delegated to an entity performing SoHO donor history review and medical examination may be indirectly performed through the auditing of the entity by the establishment receiving the SoHO and this information can be considered when assessing release procedures (*see 4.4.9*).

An inspection of donor history and medical examination/assessment inspection should focus on:

- Secure donor identification, including contact details and evidence of identity;
- Medical health and lifestyle questionnaire and confidential interview;
- Management of donor deferrals.

Training and qualification of personnel performing medical examination/assessment.

4.4.4 Donor testing

Regarding testing of SoHO donors or of persons from whom SoHO are collected for autologous or within-relationship use, depending on the situation in each MS, inspections of testing laboratories may be performed by another official agency or regulator. In this situation CAs should put in place a formal information sharing agreement with the other organisation. This will ensure that issues affecting the suitability of a laboratory to conduct testing are brought to the attention of the relevant CA.

A specific donor testing laboratory inspection may be indicated when:

- A laboratory provides services to a large number of establishments/entities;
- An inspection conducted by another regulator identifies concerns.

The inspection focus regarding testing should be on**:**

- Personnel - appropriate numbers to perform activities and training;
- Review types of testing performed, assays, platforms etc.;
- Control values; shifts and trends; out of specification results;
- Proficiency testing;
- Validation of testing processes;
- Qualification, calibration and maintenance of equipment;
- CE marking of medical devices as appropriate;
- Management of samples from receipt to reporting of results, including peer checks/quality checks, archiving of samples as required;
- Storage of test kits;
- Deferral process or confirmatory testing, as applicable for donors tested as reactive.

4.4.5 Collection

The principal objective of inspecting a collection entity is to verify that collection is carried out under conditions that protect the health of the donor and the safety and quality of the donation.

The verification of collection practices should be performed through the auditing of the collection services by the SoHO establishment.

Alternatively, CAs may organise inspections of collection entities. The document *'risk-based inspection planning of entities, third parties or third country suppliers'* can be used to determine if an inspection is required. For detailed information on conducting inspections to verify compliance with the requirements for collection see document *'Procurement/Collection of SoHO'*.

A specific collection inspection may be indicated in the following circumstances:

- Following receipt of a complaint (*e.g.* from a donor);

- When a collection entity provides services to a large number of SoHO entities/ establishments.

The inspection focus regarding donation should be to:

- Verify that all donor information and consent materials are complete, comprehensible, and approved;
- Confirm that donor files include signed consent forms, with the signature date falling within the appropriate timeframe before donation, as per requirements, and withdrawal procedures;
- Check that no advertising or promotional materials refer to compensation;
- Review compliance with national legislation on reimbursement and donor welfare;
- Verify the presence and functionality of a validated traceability system covering donors, recipients, and offspring;
- Confirm that donor–recipient–offspring identifiers are unique, secure, and confidential;
- Confirm that donor testing covers relevant infectious and genetic diseases, to the extent that National law allows for genetic testing ;
- Verify that donor health and family history reviews are thoroughly and confidentially assessed and documented;
- Ensure that procedures exist for donor–recipient genetic matching, to the extent that National law allows for genetic testing.

The inspection focus regarding collection should be to:

- Verify collection processes;
- Verify agreements between collection sites, as relevant;
- Verify that a documented contamination-control risk assessment exists and is reviewed periodically;
- Review documentation demonstrating that equipment and reagents are validated for use in relevant SoHOs and do not pose harmful effects to recipients.

4.4.6 Processing

For processing activities, the related inspection is an active onsite process, which may follow part of the donor to recipient chain or human application. A specific process inspection may be part of a general inspection or be indicated when:

- On request of an assessor regarding a request for a SoHO Preparation Authorisation;
- SoHO is recalled;
- An establishment is carrying out a process or processes that are complex, innovative or unique.

As a general principle, inspections conducted by a solo inspector should be avoided. Where this is not possible due to limited resources or other constraints, CAs should have in place procedures for mitigating the risks associated with solo inspections.

The inspection focus regarding processing should be to:

- Review premises used for activities - located, constructed, adapted and maintained to suit the activities to be carried out;
- Verify that a documented contamination-control risk assessment exists and is reviewed periodically;
- Confirm that environmental qualification and monitoring data support the chosen level of control;
- Review equipment qualification, maintenance and calibration records;
- Review documentation demonstrating that equipment and reagents are validated for use in relevant SoHOs and do not pose harmful effects to recipients;
- Review traceability;
- Compliance to EDQM monographs;
- Newly authorised preparations.

4.4.7 Quality control

Quality control inspections can include verification steps, sampling and testing. Incoming materials/SoHO, in process testing and final product testing should be considered. These are used to ensure materials, processes and the final product meet the required specifications.

Inspections in relation to quality control should include a review of any sampling plans, acceptance criteria (the EDQM monographs can provide the minimum requirements for evaluation of specific SoHO), verification that controls agreed/authorised by the CA, testing kits used and whether these are CE marked or for in house use.

Any outsourced quality control testing should be appropriately verified by the SoHO establishment. All methods of quality control should be appropriately validated for the specific SoHO.

An inspection of in-process testing could be incorporated in the inspection of processing activities.

A specific inspection of quality control measures may be indicated when:

- A significant change in processing may impact on quality control;
- An entity is responsible for quality control testing for many entities/establishments.

The inspection focus regarding quality control should be in:

- Verify the sampling and testing plans and records;
- Review maintenance and calibration records;
- Review batch acceptance of reagents;
- Review documentation related to the process for releasing results (*e.g.* peer review);
- Review statistical process control if applicable.

4.4.8 Storage

Storage procedures and storage conditions for SoHO throughout its lifecycle (from collection to human application) can be integral to the quality and safety of the final product. Procedures and equipment used as well as specific conditions for storage should be suitable for the SoHO, this should include safety instructions for personnel in relation to cryostorage. These conditions should be clearly defined from collection to human application or supply to a manufacturer of products regulated by other EU legislation.

Storage conditions should also be clearly set out for the transport of SoHO.

A specific inspection of storage may be indicated in the following circumstances:

- Upon receipt of a complaint from a clinical end-user;
- Following catastrophic failure of a storage facility;
- If an entity stores a large amount of SoHOs or provides storage for multiple entities/establishments.

The inspection focus regarding storage should be in:

- Verify that a documented contamination-control risk assessment exists and is reviewed periodically (this includes pest control of storage areas);
- Ensure that contingency plans and alarm systems are in place and used correctly to prevent any compromise to any stored SoHO;
- Review equipment maintenance and calibration records;
- Verify control of expiration dates.

4.4.9 Release

The release procedures should be reviewed. This should include a review of the responsibilities of the Releasing Officer, along with the criteria for release of each SoHO, and how it is ensured that specifications are met. The exceptional release process should also be reviewed *i.e.* when the SoHO preparation does not meet all relevant standards. Examples of documentation for routine and exceptionally released products should be viewed to check adherence to the procedures.

Note: SoHO processed for autologous use or within-relationship use, without SoHO storage, shall not require release before human application. In such cases, the SoHO preparation authorisation shall include a specification of the quality control parameters to be monitored during the processing.

The inspection focus regarding release should be in:

- Verify responsibility of releasing officer and of delegated persons;
- Verify release process, documentation and release specifications applied*;*
- Verify recall procedure.

4.4.10 Distribution

The distribution process should be reviewed, with attention paid to the number of sites distributed to, and the complexity of the process. There should be clear and agreed descriptions of roles and responsibilities between the distributing entity and the receiving entity.

A specific inspection of distribution may be indicated in the following circumstances:

- Upon receipt of a complaint from a clinical end-user.
- If an entity is distributing large amounts of SOHO or to multiple entities/establishments

The inspection focus regarding distribution should be in:

- Verify distribution process, including any storage conditions for transport and validation of transport conditions;
- Verify packaging requirements and packaging process;
- Review contracts with any third party shipping companies and responsibilities in relation to equipment used for transport, with particular attention to those who may require refrigerated or frozen transport.

4.4.11 Import

An importing SoHO authorisation is required before any SoHO is imported. The CA shall assess the application for authorisation and review the relevant information to ensure that the establishment has a system to verify the equivalent standards of quality, safety and effectiveness of imported SoHOs. An import inspection can be used to assess the procedures in place at the importing SoHO establishment to ensure that the imported SoHO are equivalent, in terms of quality, safety and effectiveness, to SoHO preparations authorised in accordance with the Regulation.

SoHO competent authorities may be required to inspect any third-country supplier which supplies SoHO to an importing SoHO establishment prior to granting or refusing the importing SoHO establishment authorisation, in particular in cases where the application concerns regular and repeated import of SoHO from the same third-country supplier.

Where the imported SoHO are not physically received by the importing SoHO establishment but are sent directly to the SoHO entity for human application to a specific SoHO recipient (*e.g.* stem cell donor registry), or to an operator for manufacturing a product regulated by other Union legislation, SoHO competent authorities may choose to carry out an inspection by means of remote document review.

A specific import inspection may be indicated in the following circumstances:

- When an inspection conducted by another CA or national regulator identifies concerns;

- When the establishment imports large volumes, and/or distributes the products to other MS;
- When the imported product is of high intrinsic risk.

The inspection focus regarding import should be to:

- Verify import authorisations issued by the competent authority;
- Ensure supplier qualification files and written quality agreements;
- Check transport validation and batch documentation for imported SoHO;
- Confirm that imported SoHO meet EU equivalent quality and safety standards and that they are listed as authorised SoHO preparations on the SoHO platform.

For detailed information on import, consult the document *'Import/Export'*.

4.4.12 Export

Export of SoHO shall only be performed by an authorised SoHO establishment. SoHO should not be exported if there is an unmet clinical need for the material in the country of origin. Exported material should be procured, used, handled, stored, transported and disposed of in accordance with the consent that has been given by the donor. SoHO should be exported only to countries that have proper controls on the use of donated material. They should be exported only for the purposes for which they can lawfully be used in the country of destination, and exporters should satisfy themselves beforehand that the SoHO will be used for a bona fide clinical application or research.

SoHO establishments shall ensure that the quality and characteristics of the SoHOs to be exported are equivalent to those of the SoHOs authorised in their own country and as required in the country of destination. SoHO establishments shall ensure that SoHO released for export comply with the requirements of the SoHO Regulation. The processes and agreements for export should be reviewed on inspection.

For detailed information on export, consult the document *'Import/Export'*.

4.4.13 Human Application

Entities applying SoHO to SoHO recipients are subject to provisions concerning traceability, reporting activity data and notifying adverse reactions or events, where relevant, and provisions concerning monitoring clinical outcomes when applying SoHO in the context of a plan for SoHO preparation authorisation. There are also obligations not to apply SoHO unnecessarily and to obtain SoHO recipient consent. Also, clinical indications are listed for the specific SoHO preparations, and these should be adhered to. However, the clinical decisions and the clinical procedures relating to human application of SoHO fall outside the scope of the Regulation and are governed by national legislation on the organisation of the healthcare of MS.

Human application can also be reviewed during a SoHO establishment inspection. This can be done by verifying the procedures in place and rules applied by the establishment to human application entities.

4.4.14 Clinical Outcome registration

Where relevant, the clinical outcome registration should be reviewed. This should review how information is transmitted and recorded in relation to clinical outcome monitoring plans. The frequency at which information is transmitted, and safety of data should be considered. If a national or international registry is used it should be verified that the registry is registered as a SoHO entity. This is also covered in the PPA process.

4.5 Inspection preparation

Competent authorities shall have documented procedures for inspectors to follow when preparing for an inspection, document *'Inspection process'* includes useful information. This will ensure that inspections are prepared and conducted in a consistent manner and in accordance with a set of performance and procedural indicators.

Once the date for an inspection has been set, an inspection team with an appropriate level of technical skills for inspecting the establishment should be allocated. As a general principle, inspections conducted by a solo inspector should be avoided. Where this is not possible due to limited resources or other constraints, CAs should have in place procedures for mitigating the risks associated with solo inspections.

4.5.1 Pre-inspection document review

The procedures for preparing for an inspection should ensure that, prior to conducting an inspection, the inspectors have familiarised themselves with the SOHO entity/SOHO establishment to be inspected by undertaking a review of all relevant information. A variety of information sources should be used when preparing for an inspection. The combination of these sources, the emphasis given to each, and the analytical approaches applied may vary, but each source should be used to corroborate and verify the other. The information to be reviewed can be found in the document titled *'Inspection process'*.

An inspector may also request a SoHO *(importing) establishment dossier* be completed and submitted by the SoHO establishment in advance of the inspection, depending on CA requirements.

Following a review of all relevant information, an inspection plan can be prepared that ensures that the key issues are addressed and the resources are used effectively during an inspection.

4.5.2 Communication prior to an inspection

An inspection will be more efficient if there is good communication with the entity/establishment before the inspection. Entities/Establishments should be provided with advanced notice of inspection information, including:

- The date, time and place where the inspection is to take place;
- The type and scope of the inspection;
- Identification of people whose presence is required *e.g.* Responsible Person, Quality Manager, Releasing Officer etc.;
- The names of the inspectors and their roles during the inspection and any relevant technical experts or SoHO assessors;
- The areas within the entity/establishment to be inspected;
- The draft timetable for each major inspection activity;
- Documentation to be made available to the inspection team;
- Timings for the opening and closing meetings;
- The office space and IT requirements;
- Approximate timings and process for issuing the inspection report.

Where possible during the lead-up to an inspection, the RP should be provided with a key contact within the inspection team. This will ensure that there is an effective flow of communication prior to and after the inspection.

A draft inspection timetable may be provided to the entity/establishment in advance of the inspection. This will allow for the relevant staff to be available at the appropriate times. It should be communicated with the site that the proposed timetable may be subject to change if required during the inspection.

Unannounced inspections may not require any communication with the site prior to the inspectors' arrival.

4.6 Conduction of an inspection

Throughout the course of an inspection, inspectors should aim to create a positive and constructive atmosphere and be prepared to answer questions but avoid entering into the role of a consultant. Although an inspector's task is to identify non-compliances, they should, where possible, include educational and motivating elements into the inspection.

During the inspection, inspectors should follow the entity's/establishment's procedures to avoid putting themselves or the SoHOs at risk (*e.g.* during an inspection of a cleanroom). Inspectors

should ensure that the conduction of the inspection does not prevent normal operational activity at the entity/establishment from continuing.

Confidential information shall be handled with integrity and in compliance with legal requirements.

4.6.1 The opening meeting

Inspections should begin with an opening meeting at which the inspection team will meet the key personnel of the entity/establishment, including the RP and Quality Manager (QM). During the opening meeting the inspection team should:

- Introduce the member(s) of the inspection team, including any technical experts or SoHO assessors;
- Confirm the inspection plan/timetable (which may be subject to change);
- Confirm the type and scope of the inspection;
- Confirm that the documentation required during the inspection is available;
- Confirm that the legal requirements for confidentiality will be adhered to;
- Explain when the identification of non-compliances will be notified *e.g.* at the time they are identified, at daily closing summary meetings or at the final closing meeting;
- Agree a point of contact to liaise with during the inspection;
- Highlight that copies of documents or other evidence may be taken off the premises (if allowed by the specific national law) and that any personal information will be appropriately redacted, and confidentiality maintained at all times.

Upon request, the SoHO establishment team should be able to:

- Provide an overview of the Quality Management System;
- Explain the organisational structure and current or proposed activities(s);
- Describe each step from collection to processing and distribution, or any other SoHO activity;
- Explain significant changes in facilities, equipment, processes and personnel since the last inspection;
- Explain how non-compliances have been resolved if this information has not already been forwarded to the CA.

A record should be kept of personnel met during the inspection (including those attending the opening and final meetings).

4.6.2 Gathering evidence during an inspection

The verification of compliance with the Regulation through SoHO supervisory activities is of fundamental importance to ensure that, across the Union, the objectives of EU legislation are

effectively achieved. SoHO competent authorities shall monitor and verify, through the organisation of SoHO supervisory activities (*e.g.* inspections), that relevant Union requirements are effectively complied with, and the technical guidelines published by the ECDC and by the EDQM or other guidelines deemed to be equivalent to them, are followed. This will involve gathering evidence from several data sources (Figure 2) to verify that the information provided in the establishment's dossier (or in the case of entities, what activities they have registered for) reflects operational practice.

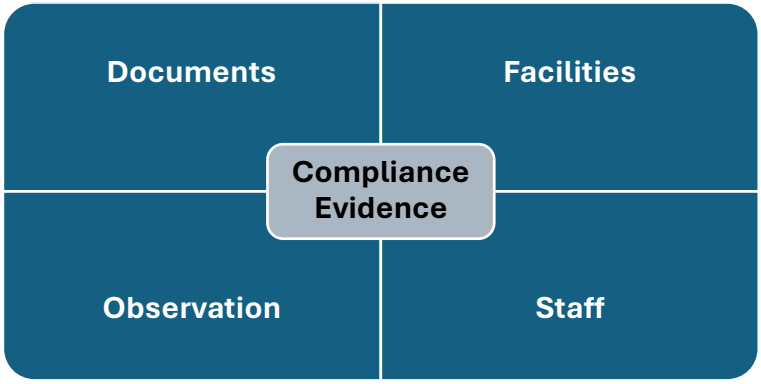


Figure 2: Evidence – data sources.

Verification of compliance may be achieved through the assessment of documents onsite, the questioning of staff to determine their competence and adherence to procedures, visiting facilities and observing the actual performance of collection, testing, processing, storage, release and distribution of SoHO (Figure 2). Inspectors may take photos/videos or take documents off-site as documentary evidence to support the identification of non-compliances, if required. This should not interfere with the process or have the potential to affect the quality and safety of the SoHO. A procedure should also be in place to permit inspectors to take samples for external quality control testing, when the evidence indicates a concern with the establishment´s quality control systems.

In rare cases, for example when there is a suspicion of fraudulent or illegal activity, products or documents may be required to be put under seal to ensure the integrity of the evidence. This is dependent on national procedures.

Specific evidence or information that will need to be reviewed will vary depending on the type of inspection being conducted, see the document *'Inspection process'* for more information.

4.6.3 Inspection of the facilities

This should include a detailed tour to see whether the lay-out and design of the facilities and equipment are suitable for the activity taking place. Any changes since the last inspection should be reviewed. Normally, inspectors follow the process flow of the activities for which the entity/establishment is or will be authorised or is registered for. Sometimes it is appropriate to concentrate on one department if there are concerns or when changes have been made to the

facilities. Relevant service areas should be considered, *e.g.* water, steam or ventilation systems and engineering support, compliance with the requirements in term of air quality cleanliness and design of the processing and storage areas.

During the tour of the facilities, inspectors should discuss observations as they arise with key personnel, supervisors and operators to establish facts, indicate areas of concern and assess the knowledge and competence of the personnel.

4.6.4 Document review

During the inspection, a review of documents relating to the authorised activities should be undertaken. The documents should be reviewed to ensure that they are up to date, controlled and approved. The types of documents that ought to be reviewed include but are not limited to:

- Organisational structure;
- Job descriptions, role of RP, physician, releasing officer;
- Staff training records, including induction training, ongoing training, refresher training, training required following prolonged absence, competency assessment;
- Documentation control and management, including management of change of controlled documents;
- Validation (processes) and qualification (materials, equipment and facilities, including IT systems);
- Preventive maintenance programmes (equipment and facilities);
- Tracking and trending of sterility testing and air quality conditions;
- Approved supplier list and supplier selection criteria;
- Third party contracts;
- Collection and processing records;
- Internal auditing system, self-inspection and corrective and preventive action;
- Management of rejection, storage and destruction of donor material in cases where it is not suitable for human application;
- Management of complaints, non-compliance/deviations, serious adverse reactions (SAR), serious adverse events (SAE), recalls;
- Change control process;
- Contingency plans for termination of activities;
- Management of traceability and vigilance;
- Data handling and confidentiality;
- Import;
- Export;
- Record-keeping: annual report on activities and annual report on vigilance;
- SoHO entity emergency plans.

Specific SOPs may be selected to verify that the practices observed are compliant with the SOPs and that staff are aware of any revisions to SOPs.

4.6.5 One-to-one meetings with staff

Conducting one-to-one meetings with selected staff (*e.g.* the quality manager; releasing officer) during an inspection is a useful method for acquiring detailed information on their role, competency and whether they receive continuous training. A one-to-one meeting with the RP will provide an opportunity to discuss any concerns they may have (*e.g.* acquiring resources to make improvements) as well as providing an opportunity to highlight to the RP any changes to legislation, standards or other matters relevant to the activities undertaken.

4.6.6 Observation of practices and procedures

Observing the operational practices of an entity/establishment is a valuable method of verifying that staff are carrying out their tasks in accordance with documented procedures and the information provided in the establishment's licence dossier (or the activities for which an entity has registered). Practices that may be observed include but are not limited to:

- Collection procedures (*e.g.* method of collection, cleaning of apheresis equipment between patient use);
- Cleanroom procedures (*e.g.* staff gowning, preparation of SoHO);
- Receipt and release procedures.

4.6.7 The closing meeting

When the inspection has been completed, a final closing meeting should be held with representatives of the entity/establishment, normally the Director, RP, QM and any officials invited by the RP, refer to the document titled *'Inspection process'* for information. During the meeting, a summary of the inspection findings should be provided; non-compliances identified during the inspection should be described clearly and a verbal indication of the classification of the non-compliances should be given. Objective evidence to support the findings, particularly critical or major, should be made available during the meeting. As far as possible, all relevant observations should be reported at this meeting so that the establishment can initiate the necessary corrective actions as soon as possible.

In the case of critical non-compliances presenting a direct risk to the health and safety of patients, CAs should delegate to inspectors the authority to request the immediate quarantine and/or cessation of supply of the implicated SoHO and, where appropriate, their recall. This will be dependent on CAs own policies, for example, the inspector may need to present the findings for internal discussion prior to requesting quarantine and/or cessation of supply.

Finally, the steps that will be taken by the inspectors following the inspection should be explained during the meeting. This should include information about the timeframe for drafting the inspection report, the process for implementing corrective and preventive actions and the follow-up procedures to verify that the actions have been satisfactorily completed.

4.7 Post-inspection activities and procedures

Competent authorities should put in place procedures for ensuring that there is a standardised process for all post-inspection activities, for more information see the document titled *'Inspection process'*. Specifically, there should be a rapid decision-making procedure for inspectors to follow when critical non-compliances are identified during an inspection.

4.7.1 Rapid decision-making procedure

When a critical non-compliance is identified during an inspection, the inspector may be able to take immediate action to prevent the entity/establishment from continuing to carry out the activity concerned. When this is not possible (*e.g.* when a risk/benefit analysis is required prior to deciding), the first action an inspector should take following the inspection is to initiate the rapid decision-making procedure. Any change to the status of the SOHO entity/SOHO establishment should be updated on the SoHO platform. The issuing of a rapid alert should be commenced if the non-compliance has the capability to affect other EU MS.

4.7.2 Inspection report

An inspection report shall be drawn up on the findings of the inspection based on the procedures of the CA and provided to the SoHO entity/establishment. A report should be drafted that could contain the scope of the inspection, the areas and activities inspected, the findings arising from the inspection including a preliminary conclusion

If non-compliances are noted in a report, they should be described clearly and be classified as either **critical, major or minor/other non-compliances**. Non-compliances that are corrected before the report is finalised should be included within the report but accompanied by a statement that appropriate corrective actions have been taken and completed.

There should be a quality control procedure in place for ensuring that inspection reports are written in compliance with the CA procedures. An example of an inspection report is provided in the document titled *'Common format for a SoHO establishment inspection report'*. This could be done via a peer review of inspection reports by inspectors who were not involved in the inspection.

The quality control should focus, at least, on the clarity of the non-compliances and their classifications (especially for critical non-compliances), the linked reference to the SoHO Regulation, technical standards and national regulations.

Once the draft report has been through the quality control procedure, it should be sent to the entity/establishment to be reviewed for factual accuracy (if required by the MSs process), a timeframe for responding to the draft report should be provided. Where substantive evidence is provided by the entity/establishment that the report contains factual inaccuracies the report should be amended, this will be dependent on the MSs process.

The final report including final conclusion should be sent to the entity/establishment within the expected timeframe, and information should be provided on the process for addressing any non-compliances identified during the inspection.

4.7.3 Managing non-compliances identified during an inspection

Procedures should be in place for the effective management of non-compliances identified during an inspection. Most non-compliances can be managed using a corrective and preventive action plan (CAPA). In this case, the entity/establishment concerned shall be requested to submit a CAPA based on an action plan within a pre-defined time limit following receipt of the final inspection report. The CAPA and the action plan should be evaluated to ensure that it adequately addresses the non-compliances and that the timelines for completing the actions are realistic and appropriate.

In the case of critical non-compliances when the risks presented are considered too high to be managed through the implementation of a CAPA, it may be necessary to initiate several actions (depending on CA procedure), for example:

- Quarantine of affected SoHOs;
- Revocation/suspension of some or all the activities until the non-compliances are addressed;
- Implementation of a specific national sanction;
- Inform other relevant agencies (national or international) of the non-compliances (*e.g.* through the rapid alerts system).

4.7.4 Follow-up of non-compliances

There should be a procedure in place that describes how non-compliances will be followed up to ensure that the agreed corrective actions have been implemented effectively. The procedure should:

- Identify who is responsible for managing the follow-up of non-compliances (*e.g.* the lead inspector);

- Describe the steps to be taken if an entity/establishment fails to address the non-compliances within the prescribed timeframes;
- Set out a process for handing over the management of an entity's/establishment's non-compliances (*e.g.* to cover a long leave of absence).

Where critical or major non-compliances were identified or where an entity/establishment has failed to address the non-compliances within the agreed timeframes, a re-inspection (follow-up inspection) may be necessary.

4.7.5 Review and update the authorisation information

The inspection report and associated action plans shall be used as evidence to inform any subsequent decision on the suitability of an establishment to be authorised or to continue to be authorised or of an entity to be registered for specific activities. Once the report has been finalised and the process for managing non-compliances has been agreed the authorisation information should be updated to reflect any changes to an entity's/establishment's status following an inspection. The SoHO platform shall be updated to reflect any changes or updates to the entity/establishment authorisation information.

Based on the inspection outcome, a CA may decide the following:

- Grant or refuse an authorisation - Indicate which SoHO and which SoHO activities are subject to the authorisation and which conditions apply;
- Assess and as appropriate authorise a proposed significant change;
- Suspend the SoHO establishment authorisation, or the authorisation of certain SoHO activities as appropriate;
- Review and revise an entity's registered activities.

The RP should be informed in writing of any decision affecting the SoHO entity/establishment authorisation and made aware of the national procedures for appealing a decision.

The final report should be saved in accordance with a documented procedure and the entity's/establishment's risk rating updated. Please refer to the document on '*Risk-based Inspection planning of SoHO Establishments*' and '*Risk-based inspection planning of SoHO entities, third parties and third country suppliers*' for information.

4.7.6 Classification of non-compliances

These Guidelines recommend the following classifications for non-compliances.

4.7.6.1 Critical non-compliance

A critical non-compliance is a non-compliance which:

- Poses a significant and direct risk to:
  - The safety of the SoHO donor or SoHO recipient and/or offspring from MAR and adversely affects their rights; and/or,
  - The quality and safety of SoHOs, or
- Poses a potential risk to public health (criticality of unmet requirement; extent to which non-compliance occurs; frequency of occurrence of non-compliance; *e.g.* one critical piece of equipment is not qualified *vs* none of the critical equipment is qualified), or
- A combination of several major non-compliances, none of which on their own are critical, but cumulatively represent a critical non-compliance.

A critical non-compliance also occurs when it is observed that the entity/establishment has engaged in illegal and/or fraudulent activities, misrepresentation, or falsification of data.

4.7.6.2 Major non-compliance

A Major non-compliance is a non-compliance which:

- Poses a potential indirect risk to public health, or
- Indicates a major deviation of the Regulation (EU) 2024/1938. and/or national regulatory requirements and or guidance (*e.g.* EDQM, ECDC) which may impact the safety of the SoHO donor, SoHO recipient and/or offspring from MAR, and/or the quality and safety of SoHOs, or
- Has the potential to become a critical non-compliance unless addressed, or
- A combination of several minor non-compliances, none of which is major on its own, but cumulatively could constitute a major shortfall or system failure and should be explained and reported as such.

4.7.6.3 Minor/Other non-compliance

A minor/other non-compliance is a non-compliance which:

- Cannot be classified as either critical or major but which indicates a deviation from good practice (GxP) which would not be expected to adversely affect the rights, safety or well-being of SoHO donors, SoHO recipient and/or offspring from MAR or pose a risk to public health or,
- May be judged as “Other” because there is insufficient information to classify it as “Critical” or “Major”.

4.8 Enforcement and inspections

CAs should have an enforcement process in place to deal with any relevant inspection outcomes. The process should be transparent. In addition to suspension of authorisation, suspension of certain activities or procedures or withdrawal of authorisation, legal actions may be necessary such as prosecution of companies or individuals. Documentation of evidence, searches of relevant premises and records and other measures should be detailed as appropriate. The rapid decision-making procedure, discussed above, can be used as part of this process.

5 Requirements and training of inspectors

References

- General responsibilities and obligations of SoHO competent authorities (art. 8).
- Inspections of SoHO establishments (art. 27).
- Inspections of SoHO entities, other than SoHO establishments, and of third parties (art. 28).
- Joint inspections (art. 29).
- Specific requirements concerning inspectors (art. 30).
- Union training and exchange of SoHO competent authorities' personnel (art. 70).

5.1 Inspectors requirements

CAs shall appoint and formally mandate inspectors to perform SoHO supervisory activities and ensure they hold official identification. Inspections shall be carried out by inspectors who meet the requirements set out in Article 30. Inspectors shall act independently and impartially and shall provide a declaration of interests, as required by Article 6(2). Inspectors may propose or order (in accordance with national arrangements) suspension or cessation of activities where necessary and proportionate to the risk detected. Moreover:

- Before inspectors take up their duties, CAs shall provide inspectors with a specific induction training. CAs shall ensure that the induction training includes at least the elements listed in Article 30(3) (inspection techniques including practical exercises, the applicable legal framework, overview of relevant Union and national inspection guidance and best practices, authorisation systems in the Member State, technical aspects of SoHO activities and national regulatory structures.
- Inspections conducted by CAs include onsite inspections, and in suitable cases remote or virtual inspections; CA should also perform follow-up inspections to confirm corrective actions are taken when non-compliance is found.
- CAs shall have, or have access to, sufficient qualified personnel and resources to carry out SoHO supervisory activities effectively (Article 8.3a).

The procedures for training and assessing an inspector should be clearly documented and assessments of competence for individual trainees should be recorded within the quality management system.

Competence assessment should cover theoretical knowledge, practical skills and behavioural competencies, and should include documented evaluation of training modules, observed activities and, where applicable, structured examinations or case-based assessments.

Inspectors shall possess a diploma/certificate or other evidence of formal qualifications in a relevant field, awarded on completion of a university course of study or a course recognised as equivalent by the MS concerned (Article 30(1)). In exceptional cases, CAs may consider that a person's considerable and relevant experience exempts that person from the formal qualification requirement (Article 30(1)). Where used, the rationale and evidence should be documented in the CA quality system/training records. Inspectors should have post qualification experience in relevant areas within a SoHO establishment; Competent Authorities; medicinal products; classified environments (engineers); health systems (quality experts); etcetera). CAs may consider that a person's experience exempts that person from above mentioned requirements. This acceptance of experience should be appropriately detailed within the quality system or training records.

5.1.1 Personal skills and attributes

Inspectors are required to draw on a range of skills and attributes to perform their role effectively. Candidate inspectors should be evaluated for their ability to demonstrate:

- Integrity, objectivity and fairness;
- Independence and impartiality;
- Ability to communicate effectively, be open-minded;
- Capacity to analyse complex information and make evidence-based judgements;
- Ability to handle challenging situations constructively, demonstrating self-confidence while maintaining tact and professional conduct.

While recruitment and selection procedures may vary between Member States in accordance with national legislation and practices, they should nevertheless include a structured assessment of both the candidate's technical knowledge and personal skills.

Whereas technical knowledge can be acquired and strengthened through training and professional experience, soft skills such as integrity, communication, and the ability to manage challenging situations in a professional manner are more difficult to develop; for this reason, personal attributes should be given priority in the selection of inspectors if possible.

Newly appointed inspectors, even when meeting the qualification and experience requirements, should receive specific induction training.

Induction training should also cover essential supporting knowledge, including confidentiality and handling of sensitive data, conflict of interest requirements, health and safety risks, use of IT systems and regulatory platforms, and secure handling and transport of biological materials where applicable.

5.1.2 Core skills

Core skills should be structured around clearly defined knowledge domains covering legislation, regulatory systems, technical expertise, quality systems, vigilance and inspection methodology

In particular, inspector training programmes should equip new inspectors with the core skills to assess compliance with EU and national legislation, beginning with an introduction to the relevant legal framework and national systems. This should cover at least:

- Regulatory systems: authorisation and licensing of establishments (assess a prescribed number of authorisation applications); procedures for authorisation of preparation processes (assess a prescribed number of preparation authorisation applications); understanding of substantial changes to authorised preparation processes and their regulatory implications; suspension or withdrawal of authorisations; organisation of national regulatory authorities and inspectorates; interaction with EU bodies and verification of registration systems; interactions with adjacent regulatory frameworks (e.g. medicines, ATMPs, medical devices).
- Healthcare and organisational structures: national healthcare system organisation; structure of SoHO organisations in the Member State; international inspection instruments; organisation and functioning of national and international regulatory systems; cooperation mechanisms between competent authorities, EDQM and ECDC.
- Technical and scientific aspects: activities and processes of SoHO establishments; biovigilance/SoHO vigilance reporting systems (for more information see the document titled *"SoHO Vigilance for inspection"*), including communication flow, application of risk-based approaches in SoHO activities, and SoHO vigilance systems covering reporting, investigation, root cause analysis, and follow-up of serious adverse events and reactions, as well as their use in risk-based regulatory and technical decision-making; principles of data integrity and validation of computerised systems used in SoHO activities.
- Preparation Process Authorisation (PPA) – specific competencies: understanding and application of the GAPP methodology for structured evaluation of preparation processes; use of risk assessment tools, including the EuroGTP II framework, for classification and proportional oversight of preparation processes; assessment of Preparation Process Dossiers (PPD), including scientific, clinical, and pre-clinical evidence supporting the preparation process; evaluation of clinical information underpinning PPA decisions, including benefit–risk considerations within the intended clinical context; assessment of substantial changes to authorised preparation processes and their impact on safety, quality, and regulatory compliance; consideration of environmental and facility control aspects relevant to preparation processes (e.g. contamination control, classified environments); awareness of new and evolving regulatory requirements related to preparation processes at European level.
- Quality and standards: Quality Management Systems (QMS); international quality management standards (ISO, EN); GXP regulations (GMP, GDP, GCP, GPG, PIC/S, EU, WHO); EU SoHO technical guidelines and relevant EDQM and ECDC guidance; understanding of how the competent authority's quality system supports inspection planning, documentation and regulatory decision-making.
- An overview of relevant EU and national inspection guidance, where applicable, and the best practices documented and published by the SCB.

- Inspection methodology: inspection techniques and procedures, inspectorate's quality management system, including practical exercises; risk-based inspection planning; preparation and reporting of inspections; follow-up of corrective and preventive actions (CAPA); handling of non-compliance and enforcement measures, including suspension or withdrawal of authorisations; participation in joint inspections and inspections in third countries, and SoHO EU platform; classification of deficiencies, application of risk-based decision-making, and linkage between inspection findings, vigilance data and regulatory actions.

CAs should ensure that trainees undertake appropriate training covering the above-mentioned knowledge domains, in order to demonstrate competence in preparing, conducting, reporting and following up inspections, verifying registration systems, and assessing applications and dossiers for the authorisation of establishments and SoHO preparation processes, including the evaluation of technical documentation and risk-based considerations.

5.1.3 Skills required to prepare for an Inspection

Training on how to prepare for an inspection should provide trainee inspectors with the skills required to prepare for an inspection. They should be trained to make objective, evidence-based decisions regarding the scope and type of inspection to be conducted (*e.g.* a general systems inspection or a themed inspection) and the technical skills needed by the inspection team. This will require training in evaluating the following information:

- Site master files (please refer to 'SoHO (Importing) Establishment Dossier';
- Risk ratings of entities to decide when and how long to perform an inspection;
- Previous inspection reports;
- External intelligence (*e.g.* an inspection report from another agency; whistleblower);
- Whether the establishment is a complex, multi-activity establishment or a simple, single activity establishment, criticality of establishment (declaration).

Trainees should also receive training on:

- Developing a practical inspection timetable;
- Allocating roles and responsibilities to support inspectors/external advisors;
- Communicating with an establishment prior to an inspection;
- Identifying documents for review during an inspection;
- Making travel and accommodation arrangements if relevant.

When preparing for inspections involving PPA, trainee inspectors should additionally be trained to:

- Critically review Preparation Process Dossiers (PPD) in advance of inspections;
- Apply structured risk assessment methodologies (including GAPP methodology and EuroGTP II tool outputs where available);

- Identify key clinical and pre-clinical data elements relevant to the authorised preparation process;
- Assess whether proposed or existing preparation processes align with authorised clinical use and regulatory expectations;
- Identify triggers for substantial change assessments requiring regulatory review.

5.1.4 Skills through observation

Trainee inspectors should observe a variety of inspections led by experienced inspectors.

Through observation trainees will develop the skills and knowledge required to:

- Manage opening and closing meetings;
- Carry out a detailed inspection of the premises, facilities and equipment;
- Perform an effective document review or examine other records;
- Evaluate the design and implementation of the quality management system;
- Evaluate compliance with the SoHO vigilance and the traceability systems;
- Gather evidence of compliance/non-compliance;
- Record evidence of inspection findings;
- Classify non-compliances;
- Effectively question staff (*e.g.* Regarding their role, training and development);
- Order or propose to the SoHO competent authority, the suspension or cessation of any procedure or activity or impose other measures, where necessary and proportionate to the risk detected.

5.1.5 Skills on post-inspection activities

Training on post-inspection activities should cover the following:

- Escalation procedures for critical non-compliances identified during an inspection;
- Drafting evidenced based inspection reports;
- Procedures for quality assurance of inspection reports;
- Issuing a draft inspection report;
- Finalising an inspection report;
- Management and follow-up of non-compliances;
- Management of complaints from inspectees in relation to inspection findings;
- Updating an establishment's authorisation status and risk-profile;
- Updating SoHO platform with relevant information.

The introductory training should be supplemented by arranging visits for trainee inspectors to SoHO establishments. This will provide trainees with a practical understanding of the operational

activities undertaken at SoHO establishments. Conflict of interest for performing the next inspection of these establishments by the trainee should be considered.

Induction training should, where feasible, be supported by a structured mentoring approach, whereby experienced staff guide trainees through legislative, technical and procedural aspects and contribute to competency assessment.

To ensure a consistent level of competence and gradual development of inspection skills, inspectors should progress through defined stages of training and qualification. Until the initial training and practical exposure are completed, inspectors are considered trainees and cannot perform inspections independently. A structured pathway from trainee to qualified inspector and subsequently to inspection lead (this could also be called a coordinator or head inspector etc.), supports both the development of technical knowledge and the strengthening of personal skills required for effective inspection practice.

Trainee inspector: Newly appointed inspectors should be treated as trainees until the CA has documented completion of induction training and initial supervised practice and should not perform inspections independently during this period. CAs should define (in their QMS) the minimum number of inspections a trainee should observe and participate in before competence sign-off (*e.g.* three observed and three participated), taking prior relevant experience into account. Before an inspector is qualified, they should be observed (*e.g.* by a qualified inspector or line manager) conducting an inspection and be assessed against the following criteria: inspection preparation; extent and depth of inspection; the ability to gather evidence and to identify non- compliances and specifically the potential for a non-compliance to present a risk to public health; the correct application of the relevant legal requirements and standards; the ability to assign appropriate classifications to non-compliances and to initiate the necessary follow-up actions; the ability to clearly communicate non-compliances and/or observations; the ability to effectively manage co-inspectors/external advisors; completion of relevant post-inspection activities.

Qualified inspector: After successfully completing the initial induction training, the inspector is recognised as a qualified inspector. At this stage, the inspector may conduct inspection activities independently on inspection but is not yet eligible to act as inspection lead.

Inspection Lead: To be designated as an inspection lead, an inspector must complete additional specialised training, as required, and must have participated in at least three inspections in the relevant field under the supervision of an experienced inspection lead. Only after fulfilling these requirements can an inspector assume the role of inspection lead.

The terms inspector trainee, qualified inspector and inspection lead used in this document do not refer to employment positions or job titles within national systems. EU Member States have diverse administrative structures, employment frameworks and qualification requirements for staff working in their competent authorities. For this reason, the terminology applied here is not intended to define or prescribe job roles, nor to define or influence national employment frameworks.

These terms describe competency levels reflecting the progression of knowledge, skills and experience needed for SoHO inspections. Their purpose is to support a harmonised understanding of expected capabilities across the EU and to provide a common framework for

training, supervision and evaluation, independent of national job titles or employment arrangements.

Accordingly, this framework focuses on competency development, not on defining official job positions. Member States may align these competency levels with their national systems as appropriate, while ensuring that all inspectors acquire and maintain the competencies needed for effective and consistent SoHO oversight.

CAs shall ensure that induction training is complemented by specialised training for inspection of specific types of SoHO establishments and by continuous training, as appropriate (Article 30(4)). SoHO competent authorities shall ensure that the specific induction training is complemented by specialised training for inspection of specific types of SoHO establishments, other relevant topics and by continuous training, as appropriate. Inspectorates should implement continuous training programmes to ensure inspectors remain up to date with scientific, regulatory and technological developments. All training should be documented, and inspectors should be qualified or certified to inspect specific types of establishments in line with the inspectorate's quality management system. Training needs analysis should be performed for each inspector to ensure appropriate competence across all relevant subject areas:

- New and emerging developments relevant to SoHO (*e.g.* donor screening methods, donor consent, testing technologies, pathogen reduction);
- Training on novel SoHO preparation authorization processes taking into account the methodology provided by EU initiatives and endorsed by the SCB;
- Participation in the Union training programmes, ensuring equal access to training materials across all Member States;
- Advances in existing processes and practices (*e.g.* biotechnology, transfusion and transplantation medicine, hemovigilance, microbiology, immunology, laboratory techniques, plasmapheresis, tissue technologies);
- Traceability and coding systems (*e.g.* application of the Single European Code (SEC) and related IT solutions). The EU platform should be reviewed for coding requirements;
- Requirements for classified areas and environmental monitoring and controls;
- Advanced inspection skills training should include, remote/virtual inspections, non-routine (for cause) inspections, risk assessment tools, inspection of IT systems and electronic records (traceability, data integrity, cybersecurity), crisis management and continuity of supply, and joint or third country inspections;
- Continuous professional development should involve participation in international workshops and education programs, PIC/S seminars, EU inspector networks, exchange programmes, and cooperation with EU bodies;
- In-service training should follow a structured process, including observed inspections, joint participation and supervised lead inspections;
- Case studies and peer learning from inspection findings across Member States;
- Detection and investigation of suspected illegal and fraudulent activities. Inspectors must understand procedures for escalation and cooperation with other regulatory, judicial or law enforcement authorities where appropriate;
- Evaluation and follow-up of notification of serious adverse events and reactions;

- Requirements for testing laboratories including, testing techniques, equipment, facilities, handling of samples and analysis;
- Application of PPA frameworks, including GAPP methodology, EuroGTP II risk assessment tool, and clinical evaluation approaches for preparation processes;
- Assessment of Preparation Process Dossiers, including clinical and pre-clinical evidence evaluation and structured benefit–risk analysis;
- Evaluation of substantial changes in preparation processes and their regulatory classification;
- Interface between SoHO preparation processes and other regulatory domains (medicines, ATMPs, medical devices);
- Advanced risk-based assessment of preparation processes including environmental and facility control considerations.

Inspector competencies should be periodically reassessed (*e.g.* every 2-3 years or risk-based), with the approach documented in the CA quality system.

Joint inspections within the EU and inspections in third countries serve different purposes but both require inspectors to operate to a consistently high standard. Within the EU, joint inspections ensure a harmonised approach to supervision and foster cooperation and mutual recognition between Member States. Joint inspections can also be used to aid inspectors to develop knowledge in SoHOs/SoHO activities which are not common in their own MS. In third countries, inspections aim to verify that SoHO entities and preparation processes comply with EU standards as a condition for import, with inspectors acting on behalf of the European Union and representing the competent authorities of the Member States involved.

Participation in such inspections is therefore limited to inspectors who have completed their initial training and demonstrated competence to act either as a qualified inspector or, where applicable, as a lead inspector. Additional requirements apply for inspectors acting as leads in third-country inspections, given the complexity and international dimension of these activities.

5.1.6 Qualified inspector (EU Joint Inspections or third countries)

To be considered qualified, an inspector shall:

- Have completed the full initial training programme and be recognised as a qualified inspector, and
- Have participated in a minimum of 2 national inspections as an active team member.

In EU joint inspections, a qualified inspector may take responsibility for inspection activities but shall not act as inspection lead.

5.1.7 Inspection Lead (EU Joint Inspections or third countries)

A lead inspector, responsible for coordinating the inspection team, preparing the inspection plan, leading interviews, and finalising the inspection report, shall:

- Meet all requirements for qualified inspector;
- Have completed additional specialised training relevant to the scope of the inspection (*e.g.* plasmapheresis, tissue technologies, IT/data integrity, risk-based approaches);
- Have participated in at least 5 inspections in the relevant field under the supervision of an inspection lead.

For third-country inspections, the lead inspector should also demonstrate knowledge of international standards (*e.g.* WHO, PIC/S) and EU import/export provisions. For further details see the document titled *'Import/Export'*.

Annex 1: Inspection Process

References

- General responsibilities and obligations of SoHO competent authorities (art. 8).
- Inspections may be performed as part of the SoHO preparation assessment (art. 20.6).
- Authorisation of SoHO establishments (art. 25).
- Inspection may be performed to SoHO entities or third parties contracted by the SoHO establishment, within the context of a SoHO establishment inspection (art. 25.2 and 45.2).
- Inspections of SoHO establishments (art. 27).
- Inspections may be performed in the context of SAR or SAE notifications (art. 33.6).
- SoHO establishments shall not carry out any activities without prior authorisation (art. 45.1).

The information provided in this document has been categorised to enable users to identify and select the category of evidence that should be reviewed according to the type of inspection to be conducted. Harmonised guidelines for assessing technical requirements defined in the EDQM/ECDC guidelines will be published and should be utilised.

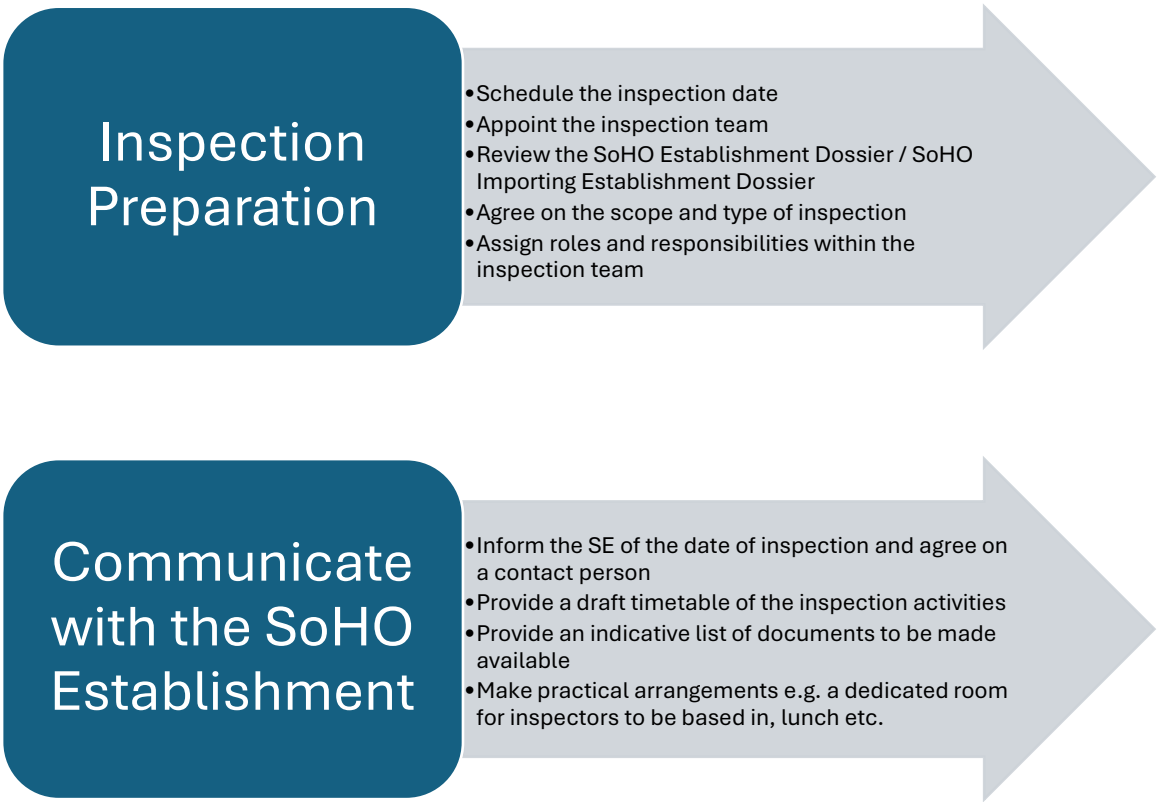
A) Overview of the inspection process

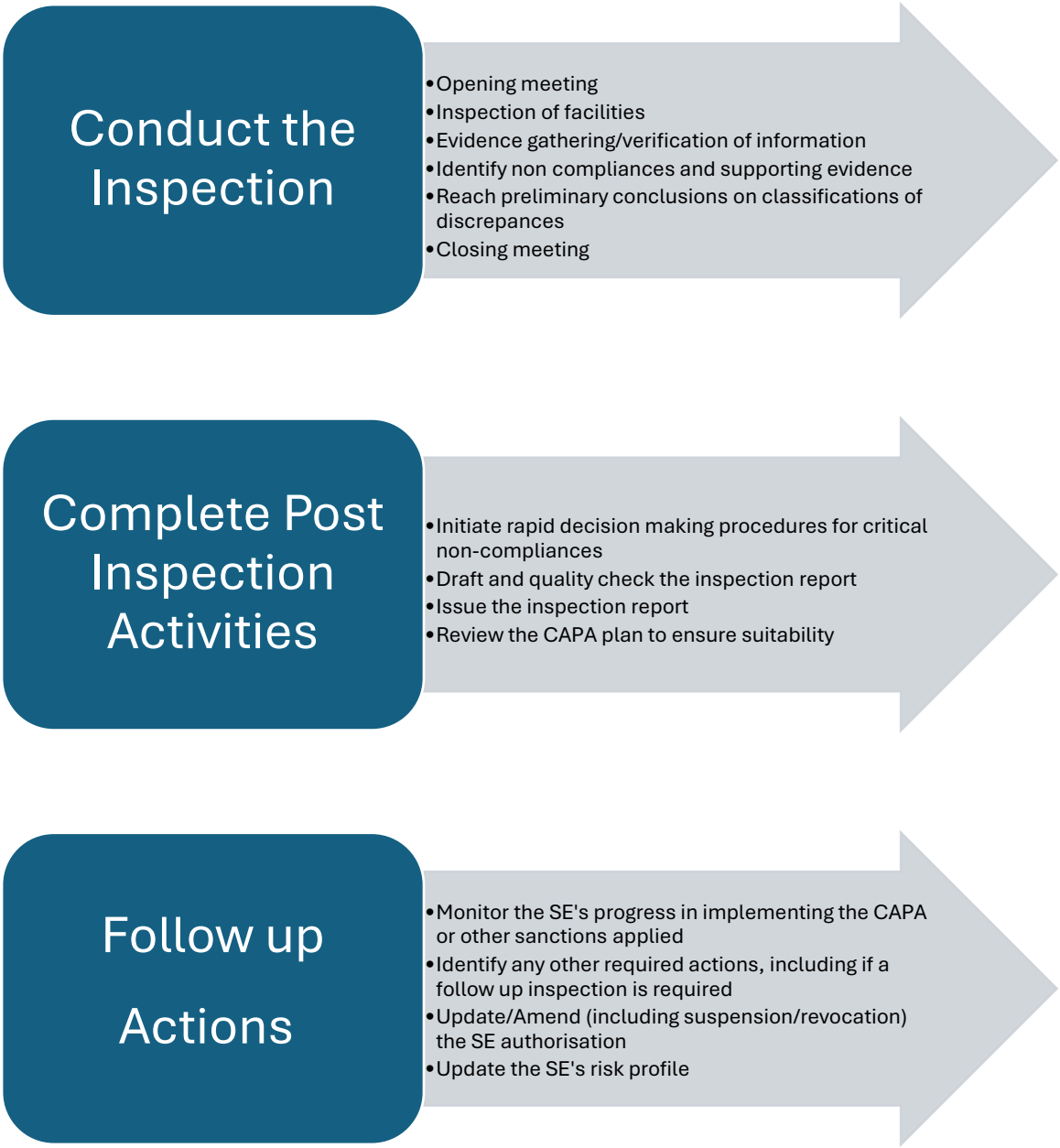
Pre-inspection document/information review

Licence Status and History	• SoHO Establishment Dossier / SoHO Importing Establishment Dossier; • Previous Inspection Report and Inspection Response; • Non-Compliances and Follow Up; • Preparation Process Dossier (where relevant); • Significant Changes Since Last Inspection *e.g.* premises, equipment, personnel or other recent variations/changes; • Any Specific Gowning Requirements Onsite which an Inspector Must be Familiar with; • Any Requirement for Vaccination of Inspectors.
Activities	• Volume, complexity and criticality; • Processes and SoHOs; • Collection and Testing Arrangements;

	• Import; • Export; • Associated Entities/ThirdParties/Sub-Contractors; • Annual Activity Data; • Emergency plans.
Other	• Serious Adverse Events and Reactions; • Recalls; • External Intelligence *e.g.* from another regulator; • Complaints/Whistleblowing; • Deviations.

Inspection Procedure Process Flow





B) General Systems inspections

The evidence reviewed during a general systems inspection of an establishment will be extensive and should include a review of the following:

Quality Management System

- QMS covers all SoHO activities for which the site is responsible for and the tasks that collectively influence the quality, safety and effectiveness of SoHOs.
- A quality manual is in place, or equivalent controlled documentation that describes the QMS.

- Personnel and organisational structure, including: organisational chart; defined roles and responsibilities (*e.g.* RP; Releasing Officer; Physician; Quality Manager); job descriptions; staff training (including retraining) and qualifications/competence; and evidence of sufficient staffing levels to carry out activities.
- Premises qualification and monitoring, including: floor plans; procedures documenting rooms/areas and their intended function; cleaning of the facility and pest control; air cleanliness levels in processing areas (where applicable); and required environmental conditions (*e.g.* light, temperature, humidity, ventilation).
- Equipment, materials (*e.g.* consumables, reagents, medical devices), and software, including qualification/validation status where applicable.
- IT systems (data processing systems), including access control, audit trails (where applicable), backup and restore, system validation/verification where required, and cybersecurity arrangements proportionate to the risks.
- Outsourced activities and contract management, including contractual arrangements and oversight.
- Processes and procedures (SOPs and associated records/forms).
- Registrations/authorisations, as applicable.
- Quality control, including testing instructions/methods for starting materials, equipment and computerised systems; and acceptance criteria/specifications for starting materials, in-process controls and release.
- Quarantine and release arrangements and procedures.
- Change management (change control process).
- Traceability systems and records.
- Complaints handling.
- Investigation and reporting of deviations/non-compliances, adverse events and adverse reactions, including corrective and preventive actions (CAPA).
- Recall/withdrawal procedures and records.
- Self-assessment and audits (internal and external), including follow-up actions.
- Validation, verification and qualification (as applicable).
- Quality risk management (*e.g.* cross-contamination management, safety measures for personnel regarding the product and nitrogen manipulation).
- Continuity planning (business continuity/contingency arrangements).
- Supply contingency and emergency planning, including arrangements for critical consumables/services, alternative suppliers or escalation routes, and emergency procedures to maintain continuity of operations.
- Tools for continuous quality improvement (*e.g.* trend analysis, KPIs), as applicable.
- Assessment of SED entries/records, where applicable.
- Data protection systems and archiving strategy.
- Contracts/Agreements/Protocols with any third party for the performance of activities or relevant steps that might have an impact on the SoHO's quality and safety.

Premises, Facilities and Equipment

- Premises (*e.g.* areas for donor selection, SOHO collection testing, processing, storage, and waste disposal) and security systems (*e.g.* access procedures and controls, ensuring that only authorised personnel can access working areas).
- Flow of personnel, equipment, and products, including SOPs for decontamination/cleaning and prevention of cross-contamination.
- Equipment, materials and software including review of process change control and, where applicable, evidence of qualification activities (*e.g.* design, installation, operational and performance qualification).
- Environmental monitoring records (where applicable), including review of processing area classification results.
- Maintenance and validation/verification of computerised systems (where applicable), including access control, audit trails, backup/restore, and incident management.
- Maintenance and calibration records for critical equipment.
- Equipment logbooks and maintenance records.

Donor testing laboratories

- Use of validated and authorised testing methods; appropriates test systems (*e.g.* screening tests, test systems appropriate for postmortal donations); compliance with applicable technical requirements; and effective systems for sample identification, handling, storage, traceability, result recording, review and reporting.
- Suitability of laboratory premises and layout for the activities performed; qualification, calibration, maintenance and monitoring of equipment; environmental controls where relevant to test performance; and arrangements to prevent contamination, cross-contamination and mix-ups.
- Application of internal quality control and participation in external quality assessment or proficiency testing schemes; pre-acceptance procedures for new batches of analytical kits; and monitoring of working standards or reference materials to detect drift over time.

Where appropriate, inspectors should:

- Follow selected donations through the testing process from receipt to result reporting.
- Verify certification, accreditation or validation status of tests in use and their application in accordance with manufacturer instructions; check system suitability tests; review validation data where test methods are modified.
- Examine equipment logbooks and maintenance records.
- Staff training (including retraining).
- When donor testing is performed by a dedicated laboratory or department (internal or external), evidence should be available that it is registered as a SoHO entity to enable appropriate oversight.
- Contracts/Agreements/Protocols when outsourced.

Procurement/Collection

- Collection/procurement procedures (*e.g.* SOPs and associated records).
- Collection/ procurement facilities (including mobile units or external collection facilities, where applicable).

- Reception procedures for supplies used by the establishment (including acceptance checks and traceability of critical consumables).
- Donor eligibility, evaluation and selection, including review of donor records and informed consent documentation, and rapid alert monitoring.
- Detailed information on inspecting a procurement organisation is provided in the Procurement/Collection of SoHO document.
- Staff training (including retraining).
- When procurement/collection is performed by a dedicated department (internal or external), evidence should be available that it is registered as a SoHO entity to enable appropriate oversight.
- Contracts/Agreements/Protocols when outsourced.

Quality Control Laboratories

- Where quality control testing/checks are performed by a dedicated laboratory or department (internal or external), evidence should be available that it is registered as a SoHO entity to enable appropriate oversight.
- Defined service agreement/contract describing responsibilities, scope of testing, data/reporting requirements, escalation, and retention of records.
- Reception procedures for supplies used by the establishment (including acceptance checks and traceability of critical consumables).
- Evidence of competence (method validation/verification where applicable, staff competence, equipment qualification/maintenance) and participation in external proficiency testing/EQA, as applicable.
- Evidence of oversight by the establishment (*e.g.* audits, performance review, deviation/CAPA interface, change notification).

Processing

- Processing procedures, including review of validation/verification data for critical processes.
- Preparation Process Dossier (or national equivalent dossier), where applicable.
- Training and competence records for staff performing processing activities.
- Quality control data for starting materials, intermediate products, and finished SOHO preparations (as applicable).
- Non-conformities/deviations recorded during processing, including investigations and CAPA (corrective and preventive actions) and effectiveness checks.
- Documentation for special processing steps (*e.g.* washing, splitting, volume reduction, leukocyte filtration, irradiation, pathogen inactivation, cell separation, concentration, purification), where applicable.
- Quality assurance results, including trend analysis where relevant.
- Maintenance, calibration, and requalification records for critical equipment.
- Reception procedures for supplies used by the establishment (including acceptance checks and traceability of critical consumables).
- Release process from the production/processing area, including defined responsibilities and documented approval.

Storage

- Release criteria and procedures, including verification of product safety and quality prior to release.
- Quarantine arrangements, including physical and/or electronic segregation, status labelling, and access controls.
- Maintenance and calibration records for critical storage equipment, including at least one item selected by the inspection team for detailed review.
- Access procedures and controls, ensuring that only authorised personnel can access stored SoHOs.
- Conformity with packaging and labelling requirements primary container, external packaging labelling) including any accompanying documents.
- Contingency arrangements for storage, including documented procedures and tested plans for equipment failure (*e.g.* in the case of dewar or freezer failure), alarm systems, emergency response and alternative storage capacity.

Note: Storage is a high-risk stage where loss of viability, contamination, mix-ups, or loss of traceability can occur. Under the SoHO framework, inspectors should verify that storage conditions, controls, and contingency measures consistently protect the quality, safety, traceability and availability of SoHO.

Transport and Distribution

- Procedures to ensure that transport and distribution conditions are defined and met.
- Calibration of temperature loggers and temperature recordings (whenever applicable).
- Packaging containers including examination of primary packaging to verify sterility where required. Labelling and validation that labels are resistant to humidity/liquid nitrogen and that are barcodes/QR codes are indelible?
- Transport validation, demonstrating that specified conditions (*e.g.* temperature, time orientation) are achieved and maintained.
- Ongoing assurance that validated transport conditions are maintained during routine operations (*e.g.* temperature recordings, temperature loggers' calibration).
- Transport arrangements, including contracts/agreements with couriers or transport service providers and defined responsibilities.
- Recall procedures, including communication pathways and roles during transport and distribution.
- System for handling returned products, including assessment, quarantine, and traceability.
- End-user agreements, where applicable, defining responsibilities for receipt, storage, use and reporting.
- Contracts/Agreements/Protocols when outsourced.

Import/Export

- Preparation Process Dossier for imported SoHO preparations from third country suppliers.

- Procedures to ensure equivalency of quality, safety, and effectiveness with the Regulation, including donor selection, testing, processing, equipment and materials, verification that donations are voluntary and unpaid, where applicable.
- The written agreement between the importing establishment and the exporter (third country supplier).
- The type of product to be supplied.
- Details of the flow of imported tissues and cells from their procurement to their reception at the importing establishment.
- Documentation describing the general quality and safety system at the third country supplier.
- Determine if the importing establishment audits its third country supplier and, if so, how this is done.
- Procedures for the management of SARE and recalls associated with imported tissues and cells.
- Verification that traceability is maintained from donor to recipient.

Additional guidance for inspecting Import/Export is provided in the Import/Export document.

Vigilance systems

SoHO entities and establishments shall implement and maintain vigilance systems covering, at a minimum:

- Traceability of SoHO from donor to recipient and vice versa;
- Reporting, investigation and management of serious adverse events and reactions;
- Recall and withdrawal procedures;
- Protection of personal data and confidentiality;
- Look-back and trace-back activities.

Detailed operational requirements are defined in 'SoHO Vigilance for inspection'.

Evidence – Thematic Inspections

For thematic inspections, evidence should focus on the selected SoHO activity area(s), for example:

- Testing (*e.g.* donor eligibility-related testing and/or SoHO testing procedures and controls);
- Transport and distribution (conditions, controls, traceability, deviation management across transport/distribution steps);
- Premises, facilities and equipment (fitness for purpose, maintenance, qualification/validation where relevant, environmental controls).

Desk-based inspections

A desk-based inspection should, as a minimum, involve a review of an updated SoHO establishment dossier/authorisation information (including any updates recorded and maintained for the purposes of authorisation). This review may be supplemented by a targeted questionnaire to obtain specific information not clearly evidenced in the dossier. Where used, the questionnaire should be concise, unambiguous and evidence oriented.

If a questionnaire is used it should be as concise and clear as possible. The following is an indicative list of the sorts of questions that may form part of a questionnaire for a desk-based inspection.

1. Have any changes taken place in the activity profile of your establishment since the last inspection?
2. Have you made any changes to any of the following processes since the last inspection?
    - SoHO donor registration,
    - SoHO donor history review and medical examination,
    - Testing of SoHO donors or of persons from whom SoHO are collected for autologous or within-relationship use,
    - Collection,
    - Processing,
    - Quality control,
    - Release,
    - Storage,
    - Distribution,
    - Import,
    - Export,
    - Human application,
    - Clinical outcome registration.

If yes, please provide details.

3. Have there been any changes to key personnel since the last inspection? (*e.g.* change of QM; RP; Physician; Releasing Officer) If yes, please provide details.
4. Have there been any changes to facilities/premises or critical equipment since the last inspection? If yes, please provide details.
5. Are any changes to staff, activities, premises, facilities or equipment planned over the next two years? If yes, please provide details.
6. Are there any changes with subcontractors/third party/supplier since the last inspection? If yes, please provide details and agreement (or project agreement).
7. Have you been inspected or accredited/re-accredited by any other regulator/accreditation bodies since your last inspection? If yes, please provide a summary.
8. Is there any other information that you would like us to take into consideration?

Annex 2: Common format for a SoHO Establishment inspection report

References

- Following each inspection, the SoHO competent authorities shall draw up a report on the findings of the inspection and provide it to the SoHO establishment concerned. Where the result of the inspection so requires, the SoHO competent authorities shall, as appropriate, set out any corrective or preventive action needed or shall request the SoHO establishment to respond with a proposal for such actions, with associated dates for completion (art 27.10).

SoHO Establishment inspection report

Complete this form by replacing the italicised text

General Information	
Report Reference No.:	
Inspected Site(s):	*Name and full address of the inspected site(s).*
Activity Summary:	*Please copy the list of authorised preparations and registered/authorised activities from the SoHO platform.*

Inspection date(s): **Inspector(s):**	*Date(s), month, year Name(s) of the Inspector(s) name(s)* *Name(s) of Expert / Assessor (if applicable)* *Name(s) of the Competent Authority(ies)*
Reference to Regulations against which the inspection is conducted:	

Brief Report of the Inspection Activities undertaken	
Introduction:	*Short description of the SoHO establishment and the activities.* *For inspections in non-EEA countries, it should be stated whether the Competent Authority of the country where the inspection took place was informed of the inspection and whether the Competent Authority took part in the inspection.* *Date of previous inspection.* *Name(s) of Inspector(s) involved in previous inspection.* *Conclusions of the previous inspection*
Scope of inspection:	*Short description of the inspection (process related inspection and/or General Quality System inspection, reference to specific SoHOs or where appropriate).* *The reason for the inspection should be specified (e.g. new SoHO establishment application, new preparation process application, routine, event related inspection, etc.)*
Type of inspection:	*On site, virtual, remote document review*
Inspected area(s)/activities:	*Short description of the area/activities, each inspected area/activity should be specified.*
Areas/activities not inspected:	*Where necessary, attention should be drawn to areas or activities not subject to inspection on this occasion.*
Major changes since previous inspection:	
Personnel met during the inspection:	*The names and titles of key personnel met should be specified here or a list should be attached.*
Overview of inspection findings from last inspection and the corrective action taken:	*Summarise previous findings and corrective actions taken (if previous findings have already been addressed in a CAPA plan, this plan could also be chosen to cross reference non solved non-compliances of the new report. This can be done at the end of the report).* ☐…n.a. ☐…All non-compliances are solved. ☐…These non-compliances were not solved within the scheduled due dates: ..... ☐…These non-compliances remained unsolved: ....

Inspector findings relevant to the inspection including non-compliances

This section can link the findings to the non-compliances and be used to explain classification.

Quality Management System	☐…Assessed during this inspection	
Non-compliance evidence	Reference to SoHO legislation/ national legislation/ national standards etc.	Indicative classification of non-compliance

Quality assurance	☐…Assessed during this inspection	
Non-compliance evidence	Reference to SoHO legislation/ national legislation/ national standards etc.	Indicative classification of non-compliance

Personnel and organisation	☐…Assessed during this inspection	
Non-compliance evidence	Reference to SoHO legislation/ national legislation/ national standards etc.	Indicative classification of non-compliance

Premises	☐…Assessed during this inspection	
Non-compliance evidence	Reference to SoHO legislation/ national legislation/ national standards etc.	Indicative classification of non-compliance

Equipment and materials	☐…Assessed during this inspection	
Non-compliance evidence	Reference to SoHO legislation/ national legislation/ national standards etc.	Indicative classification of non-compliance

Environmental monitoring	☐…Assessed during this inspection	
Non-compliance evidence	Reference to SoHO legislation/ national legislation/ national standards etc.	Indicative classification of non-compliance

Documentation and records	☐…Assessed during this inspection	
Non-compliance evidence	Reference to SoHO legislation/ o national legislation/ national standards etc.	Indicative classification of non-compliance

Traceability and coding	☐…Assessed during this inspection	
Non-compliance evidence	Reference to SoHO legislation/ national legislation/ national standards etc.	Indicative classification of non-compliance

Selection criteria for donors of SoHO	☐…Assessed during this inspection	
Non-compliance evidence	Reference to SoHO legislation/ national legislation/ national standards etc.	Indicative classification of non-compliance

Laboratory tests required for SoHO donors	☐…Assessed during this inspection	
Non-compliance evidence	Reference to SoHO legislation/ national legislation/ national standards etc.	Indicative classification of non-compliance

SoHO donation and collection procedures	☐…Assessed during this inspection	
Non-compliance evidence	Reference to SoHO legislation/ national legislation/ national standards etc.	Indicative classification of non-compliance

Control of the SoHO received	☐…Assessed during this inspection	
Non-compliance evidence	Reference to SoHO legislation/ national legislation/ national standards etc.	Indicative classification of non-compliance

Processing	☐…Assessed during this inspection	
Non-compliance evidence	Reference to SoHO legislation/ national legislation/ national standards etc.	Indicative classification of non-compliance

Quality control	☐…Assessed during this inspection	
Non-compliance evidence	Reference to SoHO legislation/ national legislation/ national standards etc.	Indicative classification of non-compliance

Storage	☐…Assessed during this inspection	
Non-compliance evidence	Reference to SoHO legislation/ national legislation/ national standards etc.	Indicative classification of non-compliance

Release	☐…Assessed during this inspection	
Non-compliance evidence	Reference to SoHO legislation/ national legislation/ national standards etc.	Indicative classification of non-compliance

Distribution	☐…Assessed during this inspection	
Non-compliance evidence	Reference to SoHO legislation/ national legislation/ national standards etc.	Indicative classification of non-compliance

Labelling for collection/procurement/ distribution (primary, secondary, external packaging)	☐…Assessed during this inspection	
Non-compliance evidence	Reference to SoHO legislation/ national legislation/ national standards etc.	Indicative classification of non-compliance

Management of SAR/SAE and recall	☐…Assessed during this inspection	
Non-compliance evidence	Reference to SoHO legislation/ national legislation/ national standards etc.	Indicative classification of non-compliance

Import	☐…Assessed during this inspection	
Non-compliance evidence	Reference to SoHO legislation/ national legislation/ national standards etc.	Indicative classification of non-compliance

Export	☐…Assessed during this inspection	
Non-compliance evidence	Reference to SoHO legislation/ national legislation/ national standards etc.	Indicative classification of non-compliance

Third Party Agreements	☐…Assessed during this inspection	
Non-compliance evidence	Reference to SoHO legislation/ national legislation/ national standards etc.	Indicative classification of non-compliance

Internal audits	☐…Assessed during this inspection	
Non-compliance evidence	Reference to SoHO legislation/ national legislation/ national standards etc.	Indicative classification of non-compliance

Computerised systems	☐…Assessed during this inspection	
Non-compliance evidence	Reference to SoHO legislation/ national legislation/ national standards etc.	Indicative classification of non-compliance

Other specific issues identified	☐…Assessed during this inspection

Conclusions	
Summary and conclusions:	*The Inspector(s) should state whether, within the scope of the inspection, and considering that inspections of legal compliance regarding the quality and safety of SoHO activities are carried out on a sampling basis, with the inspected entity being responsible for observing and maintaining compliance with applicable legal requirements, the SoHO establishment operates in accordance with the SoHO legislation and national laws. The conclusion should be stated in the final report (it is up to the CA if the conclusion is already stated in the preliminary report).*

Annex 3: Procurement/Collection of SoHO

References

- SoHO entities in charge of collection must be registered (art. 35).
- SoHO entities must collect data relating to their collection activities and submit this data to the EU SoHO platform as part of their annual report (art. 41.1).
- SoHO entities must ensure high levels of safety and protect the health of living donors before, during and after the SoHO collection (art. 52.2). This includes identifying and minimising risks, such as exposure to reagents or solutions that might be transferred to recipients and negatively affect their health (art. 53.1h and art. 58.6).
- SoHO entities must achieve a high level of assurance that pathogens that are potentially life-threatening, disabling or incapacitating are not transmitted from a third-party donor to recipients or to offspring from medically assisted reproduction (art. 58.1).
- SoHO entities must screen donors for markers of transmissible infections, in addition to conducting donor evaluation including current and past health, travel and relevant behavioural histories (art. 58.2).
- SoHO entities must consider the requirements on donor screening set out in the most recent guidelines published on the EU SoHO platform by ECDC (art. 59.4.a.i).

General considerations applicable to SoHO

Robust donor selection, evaluation and collection (including procurement) practices are crucial to ensuring that the risks associated with the use of SoHO for human application are minimised. It is essential that CAs have systems and processes for ensuring that collection takes place in accordance with the requirements of the Regulation (EU) 2024/1938. Standards for the selection and testing of donors for SoHO are contained in article 58 of this regulation, and the testing requirements are set out in EDQM guides and ECDC recommendations.

An inspection of collection activities should, as appropriate to the risk and scope of activity, include review of:

- The registration of the collection activities and the type of SoHO collected;
- The written agreement between the collection organisations (or third parties) and the authorised establishment should be reviewed to ensure that suitable controls are in place for the collection of SoHO;
- The systems in place for collection (organisational chart, job descriptions, qualification and competence of the nominated medical practitioner, training and qualification of staff);
- Procedures for decontamination and cleaning, aseptic technique used, sops in place to avoid cross contamination, etc.;

- Confirmation that the actual practices of collection are in accordance with the documented procedures;
- The instruments and materials (blood bags, apheresis sets, bottles, needles etc.) Used for collection (single use or if reusable - decontamination and sterilisation by validated techniques) and their traceability;
- Procedures for obtaining blood samples for serological and/or NAT testing of donors (included blood group serologic testing if relevant), identification and handling and shipping of the samples, assessment of the laboratory tests, or any other biological sample needed for testing (*e.g.* in the case of faecal microbiota);
- Packaging and labelling (primary, external and container) including CE mark and sterility of the primary packaging or any document of validation of this type of packaging;
- System of traceability used;
- Confidentiality and Data protection;
- Contracts/Agreements/Protocols with any third party for the performance of activities or relevant steps that might have an impact on the SoHO's quality and safety.

Within the quality management system, the inspector should check:

- Non-compliances and deviations;
- Complaints management;
- External and internal audits;
- Lists and reports of any serious adverse events or reactions and the associated corrective actions;
- Change control;
- Archives of donor and collection records;
- Recall procedures;
- Validation of procedures;
- Look-back procedures.

Donor selection requirements

Every SoHO donor is required to provide not only personal data that uniquely distinguishes them but also their medical history. Therefore, every SoHO entity should have a donor register that contains the personal data provided as well as any clinical data arising from a donation. The donor file should contain in accordance with (EU) 2016/679 and with article 75 of Regulation (EU) 2024/1938:

- Identification of the donor (first name, family name, sex, date of birth), donor identification number. It is recommended that the identity of soho donors is verified by a photo-document (*e.g.* passport, identity card, driver's licence);
- Contact details (*e.g.* address);
- Health and medical history of the donor;
- Donor questionnaire;
- Informed consent;
- Self-exclusion form (if applicable by national regulations);

- The referral process for potential donors.

Inspectors should check that the donor screening procedures and their records comply with the requirements in the regulation and the EDQM and ECDC guidelines or equivalent national guidelines regarding: donor identity, donor selection / deferral criteria, completion of a donor questionnaire, donor consent, medical history, and the identification of behavioural risks that would lead to donor deferral. It should also be verified that the donor selection process and evaluation is carried out by trained personnel and the outcome documented according to requirements of the ECDC and EDQM guidelines.

Donor file requirements are inspected by examining a representative sample of documents from donors:

- Completed donor questionnaires;
- Self-exclusion form (if applicable by national regulations);
- Donor consent form;
- Donor history (*e.g.* donation frequency, health and medical history).

Where possible the inspection should be conducted while the relevant activities are operational. This includes:

- Donor identification;
- Health examination or a simulation of these activities;
- Pre-donation testing (*e.g.* Haemoglobin, blood pressure, temperature);
- Donor history review and acceptance/deferral.

Specific risks should be evaluated, for example the risks arising from donors who have visited a country with an epidemiological concern.

Reviewing collection records

A sample number of collection records should be reviewed to ensure that they are complete and accurate. The extent of documentation reviewed should be proportionate to the type of SoHO and risk profile. The records should contain (at least) the following information:

- The identification of the establishment, name and address to receive the donations or the establishment in charge of clinical application for direct use;
- The donor identification (first name, family name and date of birth). If a mother and child are involved in the donation - the name and date of birth of the mother and the name (if known) and date of birth of the child;
- Both description and identification of the donation (including samples for quality control, where appropriate);
- The identification of equipment used for collection;
- The consent/authorisation form, where applicable;
- The identification of the person who is responsible for the collection, including their signature;
- Date, time (where relevant, start and end) and location of collection and the procedure used, including any incidents that occurred;

- Where relevant, environmental conditions at the collection facility (description of the physical area, equipment used, where collection took place);
- Date, time and identification of the person who obtained samples for biological tests, including method of centrifugation of the blood if relevant;
- The results of the testing of the living donor;
- Clinical data, laboratory test results, and the results of other tests carried out for deceased donors, conditions under which the cadaver was kept refrigerated after death (or not), time of start and end of refrigeration;
- If an autopsy was performed on a deceased donor, the results must be included in the record (for tissues and cells that cannot be stored for extended periods, a preliminary report of the autopsy must be recorded);
- The id/batch numbers of reagents and transport solutions used;
- The batch number of collection containers used (e.g. Blood bags);
- For deceased donors, the report must also contain the date and time of death.

For each SoHO procured, there must be sufficient data to ensure traceability. This includes:

- Identification of the soho entity;
- Identification of the donor;
- Identification / description of the collected soho.

A sample number of donor records should also be reviewed for completeness. Donor records should contain (at least):

- The donor's medical history;
- Results of the physical examination;
- Social behaviour and risk factors (for deceased donors, information to obtain from relatives);
- Testing and haemodilution evaluation;
- Biochemical and pharmacological parameters;
- Donor identification.

If an establishment accepts patients with positive serological test results, inspectors should check that there are appropriate procedures in place to manage the risks. Specifically, the establishment should have suitable quarantine and decontamination procedures and measures in place to protect staff and other SoHOs.

Inspection of premises and equipment

The inspection should include a visit to all the premises /areas used for collection.

During an inspection of a collecting entity, the inspector should verify that collection is performed in dedicated facilities and in accordance with procedures that minimise bacterial or other contamination. Inspectors should verify that collection is carried out by trained personnel, using qualified facilities, equipment and methods, and as described in the POs operating procedures. For living donors, collection must occur in an environment that ensures their health, safety and privacy. Where relevant, environmental conditions at the collection facility should be controlled.

The equipment and instruments used should be checked to ensure that they are qualified, and sterilised between collections, in accordance with a validated method. Sterile single- use instruments shall be used whenever possible. Aseptic techniques must be used throughout the collection procedure. Guidance relating to equipment and materials to be used during collection can be found in the EDQM Guide to the preparation, use and quality assurance of blood components 22nd edition Chapter 2 (section 2.5).

Inspection of premises and equipment will include:

- Collection and preparation areas (including mobile units and/or external facilities);
- Testing area;
- Storage areas (released, non-released, quarantine);
- Equipment for transportation;
- Storage for consumables (*e.g.* Cell-bags, test kits, labels);
- Engineering support (*e.g.* temperature control system, air conditioning / heating systems).

The inspection should also include a review of the qualification and maintenance of the equipment such as balances, apheresis machines, cell counters, centrifuges, separators, sterile connecting devices, tubing sealers, freezers, irradiators and the specialised equipment for blood grouping and infectious-marker testing, where relevant.

The inspection may focus on one area if there are concerns or special requirements.

Review of transport

The inspector should check written procedures and validation data to verify that transport (including validation data for length of time in transit) and packaging conditions (e.g. temperature monitoring) are validated and in place. (See Appendix 6 of the EDQM Guide to the preparation, use and quality assurance of blood components 22nd edition for an example of a transportation validation).

They should examine a selection of packaging containers and their labels and observe their suitability and sterility (primary packaging) and whether the integrity and required storage and/or transport conditions of the tissues or cells are maintained.

Donations from deceased donors

The inspector should check:

- The annual activity report with focus on the number of deceased donors per year (data should be available from annual activity returns);
- The written agreement signed between the procurement organisation(s) and soho establishment and if relevant with third parties;
- Donor (or donor family/legal representative) consent in accordance with national regulations; records should indicate how the consent has been obtained. Telephone interviews to obtain consent should be avoided. If consent is obtained by telephone, the

inspector should ensure that there are robust procedures in place for identifying the person giving consent and documenting the nature and scope of the consent given;

- The procedure for deceased donor evaluation and the donor's suitability. This may include a combination of the following information sources:
    - The medical records of the donor;
    - An interview with a person who knew the donor well;
    - An interview with the treating physician;
    - An interview with the general practitioner;
    - The autopsy report.
- That the collection entities (including procurement of surgical residues) have been identified and are suitable. Inspectors should verify that the area of access is restricted and that a local sterile field using sterile drapes is provided;
- That blood samples are obtained prior to death or if not possible, within 24 hours of death in accordance with applicable edqm guidance and national requirements;
- That appropriate investigations are carried out to ensure that blood samples used for testing are not diluted by prior transfusions or infusions which could make the test result invalid;
- The dedicated area where the tissues are stored prior to transfer (including temperature control);
- Documentation that accompanies the tissues to the soho establishment or the clinical end user in the case of direct use.

Specific considerations for gamete collection

Assisted reproductive technology may be undertaken either between persons in an intimate physical relationship (within-relationship use) or with the involvement of third-party donors; in both cases, fully informed written consent is mandatory. Donors shall receive clear and comprehensive information on the health and emotional risks associated with gamete donation, including, where applicable, controlled ovarian stimulation (including the risk of ovarian hyperstimulation syndrome), sedation, risks related to oocyte retrieval procedures, and potential psychological consequences of donation.

Donors (both within relationship and third-party donors) should be subject to medical evaluation and screening. In the case of third-party donations, thorough and detailed procedures should be in place for the evaluation of genetic risk factors, medical history, age of the donor and the results of the serological and/or nucleic amplification technique (NAT) screening as described in the EDQM guidelines.

The medical evaluation should also ensure that the donation / collection process does not cause harm to the health of the donor.

Third-party donations

Inspectors should review the following:

- Procedures on assessment of selection criteria for non-partner donation, including testing requirements;
- A sample of non-partner donation records. This review should include verification of the donation legislative limits (*i.e.* maximum limit of donation, age of the donor, genetic screening for autosomal recessive genes known to be prevalent, to the extent that national law allows for such genetic testing, the donor's ethnic background and an assessment of the risk of transmission of inherited conditions known to be present in the family and other genetic evaluation to the extent that National law allows for such genetic testing;
- An assessment of any potential health risks (*e.g.* superovulation/ovarian hyperstimulation, sedation and the risks associated with the egg collection procedure in an egg donor).

Within-relationship use

For each couple, the record should contain:

- The ID coding system for each couple, cycle and link of each partner's gametes to the other or donor gametes and with any resulting embryos;
- An assessment of any potential health risks (*e.g.* Superovulation/ovarian hyperstimulation, sedation and the risks associated with the egg collection procedure).

Collection report

For both within-relationship use and third-party donations, a collection report shall be prepared containing at least the following information:

- The description and identification of procured gametes (including samples for testing, where appropriate);
- The number and identification of the oocyte collected;
- In the case of sperm collection, date, time and ID of the sperm straw.

Where sperm is procured at home, the collection report shall state this and contain the following information:

- The name and address of the establishment to receive the sperm;
- The donor identification;
- Date and time of collection;
- The declaration signed by the donor stating it is his sperm;
- Confirmation of receipt and person who took possession/received the sample at the collection site and time of receipt.

Collection facilities

Inspectors should check that the collection of oocytes is performed in an appropriate environment *i.e.* operating theatre, by educated and trained personnel and in accordance with the methods described in the establishment's standard operating procedures.

Establishments should have a suitable dedicated area for sperm collection. In the case of sperm collection at home, there should be information made available to the donor on how to perform collection and the timing and method for transporting the sperm to the establishment.

Traceability

The system for ensuring traceability of gametes should be closely reviewed, with specific attention paid to the movement of the gametes *e.g.* from collection to petri dishes for counting, and movement to subsequent dishes for manipulation. Special attention should be paid to each step of the process to ensure that the linking of the gametes with the patients is maintained throughout. Each critical phase should be identified and monitored by a witnessing system (another person or electronic systems).

Specific considerations for blood and blood component collection

The following should be taken into account for inspecting the donation and collection of blood and blood components:

- Donor Selection
  The eligibility of each donor should be appropriately assessed (at every attendance) to ensure the quality and safety of blood and blood components. Inspectors should ensure that blood and blood component donors are selected and evaluated in accordance with defined eligibility and deferral criteria.
  It is important for the inspector to verify that appropriate deferral criteria are implemented in response to particular epidemiological situations (*e.g.* disease outbreaks). These deferral criteria should be developed in accordance with the most up-to-date assessments, guidance and communications regarding the situation.
  Other factors to be considered by the inspector when assessing blood and blood component donation procedures include blood and blood component donation frequency and blood and blood component donation volume. There should be defined limits established by the SoHO establishment in accordance with applicable national regulations or, if these do not exist, in accordance with the relevant EDQM guidelines.
  The inspector should ensure that there are appropriate procedures in place for other donation types as required, including; granulocytes apheresis, donations of red cells for anti-Rh D immunisation, directed and designated donations.
- Collection
  Donors should be positively identified (by providing their name, date of birth and permanent address), and identification confirmed at registration, eligibility assessment and donation. Inspectors should ensure that the identity of donors is appropriately recorded and linked to the donation record, collected blood, every intermediate and final blood components and samples.

During the inspection, the inspector should check at the minimum:

- Haemoglobin testing;
- Arm disinfection (*e.g.* materials used, expiry date of disinfectant once opened, minimum time disinfectant applied);
- Phlebotomy procedure (including equipment, inspection of bags, etc.);
- Validated disinfection procedure;
- Process for dealing with any donor adverse reactions from beginning of the procedure till after collection (*e.g.* faints, hematomas etc.);
- A suitability assessment of the location of any mobile site performed periodically and in accordance with the CA's risk-based planning, and confirmation that this was completed within the appropriate timeframe;
- Storage area for blood, blood components and consumables;
- Temperature monitoring of clinic and blood, blood components and consumable areas;
- The transport of blood from the mobile clinic to the SoHO establishment.

Annex 4: Import/Export

References

- Authorisation of importing SoHO establishments (art. 26).
- Implementing Act on Import (not yet adopted when guidelines were published).

SoHO - Inspection and verification of compliance with requirements

Three types of inspections are possible:

- Inspections of importing soho establishments (hereinafter "ises");
- Inspections of third country suppliers (hereinafter "3css") or entities subcontracted by that supplier;
- Inspections of exporting soho establishments.

Only ISEs authorised as an importing SoHO establishment can import SoHO from third countries (plasma for the manufacture of medicinal products exempted, according to article 47.2). Inspections of ISEs may be carried out as part of a general inspection of an establishment or as a themed inspection focussing on its import activities.

The evidence that should be reviewed for this type of inspection is addressed in Annex 5.

The inspection procedures to be followed depend on which type of importation arrangement is in place between the ISE and 3CS.

There are two types of importation that may be undertaken:

- Routine importation;
- Import for immediate human application to a specific soho recipient on a case-by-case basis.

Routine Importation

Inspections of ISEs should include a review of the documentation relating to the assessment made by the ISE of the quality and safety systems at its 3CS. This should cover the:

- Documentation describing the general quality and safety system at the 3CS (*e.g.* Organisation chart, staff training, facilities, processing methods, validation studies, systems of traceability and vigilance, licences and accreditation, etc.);
- Documentation relating to the review of the safety and quality of individual batches/units/preparations of soho (*e.g.* Confirmation of donor consent, confirmation of donor sample testing performed and their results, donor suitability, description of the soho, transport arrangements, etc.).

The full list of documentation required for importation is listed in Annex I and Annex II of the implementing act on import (not yet officially published when these guidelines came out).

The inspector should examine the written agreement in place between the ISE and its 3CS to verify that the roles and responsibilities for both parties are clearly defined in relation to the import arrangement. When examining the written agreement, the inspector should also verify that it includes all the required minimum contents as laid down in Annex I of the Implementing act on Import, of the Regulation.

From the documentation provided by the ISE and the written agreement in place between the ISE and its 3CS, the inspector should:

- Determine how the ISE ensures the equivalence between the imported soho, including soho preparations, in terms of quality, safety and effectiveness, to soho authorised in accordance with Regulation (EU) 2024/1938;
- Verify the prescribed activities performed by the 3CS and the details of any sub-contractors used by the 3CS in carrying out these activities;
- Evaluate each activity taking place at the 3CS (or sub-contractor), including:
    - The criteria used for donor recruitment, assessment and selection, how consent is obtained, confirmation that the donation was voluntary and unpaid or not;
    - Donor screening policy, information on the testing centre and the tests performed;
    - Methods used during processing, validation of critical processing procedures;
    - Description of facilities, equipment and materials and criteria for quality/environmental control;
    - Conditions for release of tissues and cells at 3CS;
    - Arrangements for the transportation of the tissues and cells.
- Determine the procedure for the management of SARE and recalls associated with imported tissues and cells;
- Determine how traceability is maintained from donor to recipient.

Importation on a case-by-case basis or importation in emergency situations

SoHO CA may authorise imports of SoHO for immediate human application to a specific SoHO recipient, when clinically justified, on a case-by-case basis or in emergency situations for immediate human application to SoHO recipients whose health would be seriously endangered without such an import of SoHO. In those situations, the implementing act on import gives Member States the discretion to not apply the documentation requirements for importation and the requirements for written agreements between the ISE and 3CS. In such situations, Member States must have suitable national measures in place to regulate the import and ensure traceability from donor to recipient and vice versa and that the SoHO are applied to the intended recipient.

In the above-mentioned cases, the inspection should include an examination of the ISE's documented evaluation of the safety and quality of the SoHO imported. Of particular importance in the case of one-off importation is:

- The reason why the import is required;
- Verification of the documentation related to traceability from donor to the recipient;
- The procedures in place to ensure that soho imported on a one-off basis are applied to their intended recipients;
- Verification that this import would not take place on a regular or repeated basis.

Third Country Supplier Inspection Procedures

Generally, inspections in third countries should be conducted following the general guidance on inspection procedures contained in these Guidelines. In addition, the guidance below is particularly relevant for inspections of 3CS.

Before the Inspection

When a CA decides to inspect the activities of a 3CS, preparation for the inspection should include informing the relevant authority in the third country, obtaining any necessary permission and legal requirements prior to departure. Additionally, an inspector may choose to inform the ISE(s) concerned that one or more of their 3CS will be inspected, unless an unannounced inspection is planned.

Where appropriate, an invitation should be extended to the relevant national CA to participate in the inspection. Where the 3CS to be inspected exports SoHO to ISEs located in more than one MS and/or MS CAs wish to pool inspection resources, joint inspections could be organised. Alternatively, another Member State may request that an inspection takes place. In this situation, agreement should be reached on how the requesting MS's inspector(s) will participate in the inspection.

Before the inspection at the 3CS, the inspector should investigate whether:

- There is any additional information available from a trusted source (*e.g.* An inspection recently performed by another MS);
- The site of the 3CS was recently inspected by a third country authority with a favourable or unfavourable outcome;
- The 3CS has been authorised, licensed or accredited by its national CA or if it is exempt and for which activities and for which soho or soho preparations;
- The 3CS is a member of, or applying for membership of, any accrediting organisation, or if it has been accredited in the past;
- Documentation will be available in a language known to the inspector and agree on a mutually acceptable language for the inspection or the need for an interpreter to be present.

During the Inspection

During the inspection of the 3CS, the inspectors should cross check the documentation in place at the 3CS, with any documentation and /or detailed information provided by the ISE / trusted source / third country authority, including verification:

- Of the (export) authorisation and its scope;
- That the written agreement accurately reflects the one provided by the ISE;

- That the procedures relating to prescribed activities, performed by the 3CS or subcontractor, are in accordance with the detailed information provided by the ISE.

In addition, the inspector should:

- Perform a detailed tour of the facilities to assess the specifications of the areas where the soho are procured, processed and temporarily stored prior to distribution and transport to the ISE;
- Review the information provided in the documentation which accompanies the exported SoHO (*e.g.* Who should be contacted in case of SAE/SAR and the accuracy of the information provided to the end user);
- Determine the number of donors per year from whom the 3CS procures and/or processes soho, if applicable. Inspectors may cross-check at random clinical and biological data or any other relevant data on the donors against the donor records in the ISE;
- Select several donor records at random to confirm that the 3CS or its sub- contractor complies with the donor exclusion criteria laid down in the relevant EDQM guide. This review should confirm that the donor's behavioural history (of relevance to increased risk of disease transmission) has been reviewed. Attention should be paid to tumours, infections and risk factors for transmissible diseases;
- Review the donor screening policy, information on the testing centre(s) and the tests performed and verify whether the tests meet ECDC testing standards.

Export of SoHO

Only SoHO establishments authorised for this purpose shall export to third countries. Inspections of this activity should address the following points:

- Verification that only SoHO meeting the requirements of the SOHO regulation are being exported for human application;
- A representative number of donor and collection records should be reviewed to ensure that equivalent safety and quality standards are applied to the SoHO concerned
- Where SoHO not meeting the normal requirements are exported on the basis of a risk assessment and exceptional release, this should be reviewed to ensure that the risk assessment was conducted adequately, release was appropriately performed and that all relevant parties involved were aware of any non- compliances and agreed to the risk/benefit analysis.

Annex 5: SoHO Vigilance for inspection

References

- Scope (art. 2).
- Definitions (art. 3).
- Inspections of SoHO establishments (art. 27).
- Vigilance (art. 33).
- Quality management system (art. 37).
- Traceability and coding (art. 42).
- Vigilance and reporting (art. 44).

Introduction

This Annex is dedicated to SoHO CA inspectors who perform SoHO entity inspections (general system inspections and/or thematic, such as vigilance).

SoHO vigilance means a set of organised surveillance and reporting procedures relating to adverse reactions and adverse events (art. 3 (42)). SoHO vigilance facilitates continuous improvement of organisation, procedures, processes within the entities and coordinated connection between all stakeholders/actors engaged in surveillance activities.

The organization and implementation of procedures for the collection and reporting of SARE within the vigilance framework may differ across regulatory authorities. The overall governance, coordination, and supervision of the SARE reporting system should be established in national legislation to ensure efficient and effective coordination between all the CAs involved to guarantee consistency and effectiveness of the SoHO vigilance activities performed, taking into account the relevant best practices documented and published by the SCB (art. 33).

At the level of the SoHO CA there should be comprehensive procedures (SOPs) and data systems for the collection of SARE reports, corresponding risk assessment, recalls, managing of Rapid alerts and collaboration with CAs responsible for vigilance under other SoHO related legal frameworks (Medical Devices (MD) and In Vitro Devices (IVD), medicinal products, including ATMP, organ transplantation). It is recommended to develop data systems in a way to allow sorting and filtering of reported SAREs hereby allowing vigilance officers to identify trends and emerging risks in a timely and systematic manner.

Legal background

SoHO entities shall maintain a system for detecting, investigating recording and reporting information concerning adverse reactions and adverse events, including those detected during clinical-outcome monitoring as part of a SoHO preparation authorisation application (art. 44.1).

In the case of SoHO collected for the purposes of manufacturing medical devices, regulated by Regulation (EU) 2017/745, medicinal products, regulated by Directive 2001/83/EC, advanced therapy medicinal products, regulated by Regulation (EC) No 1394/2007, or investigational medicinal products, regulated by Regulation (EU) No 536/2014, the provisions of SoHO vigilance also apply to the processes of donor selection, testing, SoHO collection/procurement and controls of the collected/procured SoHOs (art. 2.6).

Inspection preparation for evaluation of vigilance and traceability systems during inspection of entities

The inspections shall include the verification that SoHO entities comply with the standards, or elements thereof, including those relating to vigilance (art. 27.6).

During definition of team of inspectors, the necessity of expert involvement should be evaluated, especially in case of thematic vigilance inspections.

Before carrying out inspections (in the preparatory phase), SoHO CA inspectors should consult the SoHO CA's vigilance officer responsible for the respective entity/establishment to:

- Be made aware of non-conformities in the vigilance behaviour/practices of soho entity, in particular:
    - Completeness of preliminary assessment of SARE (imputability/seriousness) and completeness of the final investigation report;
    - Communication to soho CA information regarding any serious incident and Field safety corrective action regarding MD/IVD;
    - Providing information regarding SARE to other soho entities engaged or otherwise possibly affected;
    - Submitting the annual SARE report timely and complete.
- Be made aware of any trends in SARE reports detected by the soho CA vigilance officer;
- In case of thematic vigilance inspections, gather preliminary information about the SARE;
- Give additional attention to the areas of vigilance and traceability systems that are concerning to the soho CA vigilance officer.

SoHO CA inspectors may task the SoHO CA vigilance officer to provide additional vigilance and traceability data if deemed necessary for the specific inspection.

The SoHO CA vigilance officer may task SoHO CA inspectors to collect additional vigilance and traceability data if vigilance officer deems this necessary and it is feasible during this specific inspection.

Performing inspection on site

SoHO CA inspectors of SoHO entities shall evaluate compliance with the vigilance and the traceability systems at the SoHO entity (art. 27.8e). Importing SoHO entities shall ensure an equivalent level of traceability with regard to imported SoHO (art. 42.1).

During general systems inspections it may not be possible to explore vigilance and traceability systems in depth. In the following list the topics marked with bold should be covered during

general systems inspection and regular text topics should be inspected additionally in thematic vigilance inspections:

During the inspection the SoHO entity's QMS (art. 37) should be examined to see if QMS documents are detailed enough to provide a reliable system for SARE detection, detailed incident records, comprehensive investigation, CAPA, reporting and CAPA efficiency review/analysis. SOPs can be provided to inspector in advance before on-site inspection. Recommended to review some or all from the following:

- Vigilance SOPs
    - Detecting and documenting donor and recipient adverse reactions and adverse events;
    - Investigating SARE incidents (including ones reported by contracted entities) and determining serious (reportable) cases (including look-back procedure);
    - Risk assessment of SARE incidents.
    - Withdrawal of soho from the inventory of released SoHOs and recalls;
    - Reporting to soho CA (are contact details of CA available, are time frames acceptable?) And information exchange with other involved entities (third parties, CA of other legislative frameworks);
    - CAPA, including assessing efficiency;
    - Root Cause analysis (RCA) and/or other tools (HACCP, FMEA, MIRCA).
- Traceability SOPs
    - Donor registration;
    - Donor unique identification/coding;
    - Single European coding (SEC), if applicable;
    - SoHO identification from procurement through all procedures all the way to the distribution for human application (applicable to the extent of activities performed by the soho entity);
    - Record retention and data integrity regarding traceability and vigilance.
- Organisation
    - SOP or chart for reporting lines of personnel involved in soho vigilance activities (detecting-reporting, investigating);
    - Management responsibility for vigilance (including risk assessment, audit plans and reports, management review).
- Personnel
    - Requirements for qualifications of personnel involved in vigilance. Are there any criteria set for different roles and responsibilities regarding soho vigilance?

On-site inspection is aimed to find whether the above QMS documents are adhered to and see if vigilance is used to learn and improve SoHO entity activities. For this SoHO CA inspectors should:

- Examine whether the personnel involved in vigilance is familiar with the relevant QMS documents (evidence of working through SOPs in section A and B)?
- Identify new personnel involved in vigilance and review their training and competence assessment records. Is relevant continual training provided to all staff and is it recorded?
- Review the training of staff from reporting entities (staff of collection/procurement organisations and/or human application/end user entities), if applicable.

- Examine if vigilance personnel responsibilities are stated in the job description, is detecting and reporting of SARE covered. How entity handles situations where responsible person for vigilance is away from work (holiday, sick, etc.)?
- Review performed audits and planned audits. Is vigilance a part of any audit? Can you find evidence that management has reviewed vigilance audit findings? What kind of decisions have been taken?
- Examine the list of deviations, non-conformances and corrective and preventive actions (CAPAs) at the SoHO entity for possibly reportable SAREs and their reporting to the SoHO CA. Are reportable SARE recognised by the vigilance personnel (clinicians, partner entities, entity staff)?
- Check one or more SARE cases - is the information necessary for investigation report collected effectively and in a comprehensive manner; is the timeline for SAEs and SARs (from detection to quarantine, investigation and recall) commensurate with the risks for donors and recipients; is the timeline for reporting to partnering entities and CAs (including CAs of other legislative frameworks) commensurate with risks for the donor and patients ; Is the follow-up taken on reported incidents?
- Check whether the information on the SARE or Rapid alert received by the SoHO entity is complete, whether additional information was requested if necessary, and check whether the entity has taken appropriate actions. Are systematic methods (e.g. root cause analysis, FMEA, etc.) applied for unwanted incidents according to SOPs? Review complex adverse events (if available) to check methods applied.
- Are traceability SOPs followed? Let the staff explain the processing of SoHO and try to find gaps in the identification chain. Is there a possibility of SoHO mix-up because of insufficient marking or inappropriate handling of SoHO. Check processing records and see if you can identify unambiguously personnel involved, equipment used and that the SoHO is clearly identified according to identification SOPs.
- Check if each of SoHOs from donor or the person from whom SoHOs are collected/procured for autologous, or within-relationship use is traceable to the recipient(s) of the specific SoHO and to all the documents, samples, SoHO preparations and SoHO entities that are associated with that SoHO at any point (applicable to the extent of activities performed by the SoHO entity).
- Perform a traceability exercise: mark the unique identification code of a SoHO (*e.g.*, during premises walkaround). Can you trace everything required to that SoHO? Ask to be presented donor's signed consent for that particular donation, donor testing results, identify staff and materials involved in the processing of that particular SoHO. Who and when released that particular SoHO (was releasing staff member authorized to release SoHO)? Can the recipients be identified (if appropriate to the SoHO entity inspected) for this particular SoHO. For MAR, how many children have been born from MAR procedures using the SoHO from this particular donor?

Considering the complexity and critical nature of healthcare operations, a comprehensive approach often involves using a combination of these tools:

- HACCP - principles can be adapted for infection control and patient safety;
- FMEA - can be applied to analyse processes and identify potential failures in clinical workflows;

- Root Cause Analysis (RCA) - is valuable for investigating donor or patient safety incidents and determining the underlying causes;
- Risk Mitigation Strategies and a Risk Register - can be utilized for ongoing risk management and maintaining a proactive stance;
- MIRCA tool – can be used in case of microbial contamination.

After inspection

In addition to routine tasks and activities, after inspection on site:

- In case of thematic vigilance inspection, provide the inspection report to the SoHO CA vigilance officer;
- Discuss the inspection results and determine whether a re-inspection is required following the completion of the entity's CAPA report, liaise with the SoHO CA vigilance officer to assess acceptability of the CAPA report;
- To consider any adjustments based on the risk assessment in the interval of reinspection (based on risk assessment agreed between SoHO CA inspectors and the SoHO CA vigilance officers).

Annex 6: Inspection of Medically Assisted Reproduction (MAR) establishments

References

- Scope and definitions (art. 2 and art. 3).
- Responsibilities and obligations of SoHO competent authorities (art. 8).
- Authorisation of SoHO entities and establishments, and quality management systems (art. 25 and art. 37).
- Vigilance and reporting of serious adverse events and reactions (art. 33 and art. 44).
- Donor protection, including voluntary and unpaid donation (art. 53).
- Information and informed consent of donors and recipients (art. 55).
- Donor eligibility, testing and release of SoHO (art. 58, art. 59 and art. 60).
- Confidentiality and data protection (art. 75).

Scope - What Is Covered by the Regulation

In the context of Medically Assisted Reproduction (MAR), the SoHO Regulation (EU) 2024/1938 applies to human sperm, oocytes, ovarian and testicular tissue, whether intended for MAR procedures or for the restoration of endocrine function, are covered under the term "reproductive SoHO". Embryos, although not directly retrieved from the human body, are also included within this definition.

The use of reproductive SoHO between persons who share an intimate physical relationship is referred to as "within-relationship use". In such cases, partners are not regarded as donors under the Regulation. Conversely, third-party providers are considered donors and are therefore subject to all provisions on donor protection, including eligibility assessment, consent, testing, and vigilance requirements.

The individual to whom reproductive SoHO is applied in a within-relationship procedure, such as the female partner undergoing intra-uterine insemination (IUI) or embryo transfer (ET), is considered a SoHO recipient for the purposes of this Regulation.

Typical reproductive SoHO establishments are MAR clinics and gamete banks.

Donation Principles and Consent

All donations of SoHO shall be voluntary and unpaid, some compensation may be foreseen as permitted by national law and following the *'Guidance on compensation criteria'* from the SCB.

All donors shall provide free, informed, and documented consent prior to donation. They must receive clear, comprehensive information about the nature, purpose, and potential risks of the procedures, including their right to withdraw consent at any time prior to collection/use without consequence. The public advertisement or promotion of financial compensation for SoHO donation is strictly prohibited.

The inspection focus should be on:

- Verify that all donor information and consent materials are complete, comprehensible, and appropriately approved and signed by the responsible person providing the information;
- Confirm that donor records include properly documented, signed consent forms, as well as clearly defined procedures for consent withdrawal;
- Ensure that no misleading information, advertising, or promotional materials refer to financial compensation for donation;
- Review compliance with national legislation on reimbursement and donor welfare.

SoHO Entities and Establishments

Any legal entity performing one or more of the defined SoHO activities is considered a SoHO entity. This includes MAR clinics, as well as laboratories performing analytical testing (such as serological or genetic screening, to the extent that National law allows for genetic testing) of potential donors or persons from whom SoHO are collected for within-relationship use.

The inspection focus should be on: Review documentation demonstrating that the Quality Management System (QMS) covers all authorised SoHO activities, including import and export where applicable.

Protection of Recipients and Offspring

The protection of reproductive SoHO recipients and offspring is a central objective of the Regulation, extending beyond donor safety alone. Each SoHO entity and establishment shall implement documented risk-prevention and mitigation strategies addressing communicable diseases, genetic conditions, contamination, and other avoidable risks to health, safety, and dignity.

To prevent the transmission of serious genetic conditions from donors to offspring in MAR, SoHO entities must review the donor's health and family history, referring for further assessment where necessary. Donors shall undergo genetic testing where indicated and to the extent that national law allows for genetic testing, based on risk assessment and in accordance with national legislation, as part of procedures to prevent the transmission of serious genetic conditions. Donor–recipient matching must be performed where genetic compatibility is clinically significant and to the extent that National law allows for genetic testing.

SoHO entities must maintain high standards of practice, ensuring that SoHO are handled, processed, and stored in a way that prevents contamination, maintains quality, and preserves clinical effectiveness, particularly in the context of MAR, where the probability of pregnancy and live birth reflects the effectiveness of the applied SoHO.

The inspection focus should be on:

- Confirm that donor testing covers infectious and genetic diseases in line with Article 58 and national legislation;
- Verify that donor health and family history reviews are documented;

- Ensure that procedures exist for donor–recipient genetic matching, to the extent that national law allows for genetic testing;
- Check that contamination-prevention measures are implemented (*e.g.* High Efficiency Particulate Arrestance (HEPA), volatile organic compound monitoring (VOC), aseptic handling);
- Review documentation demonstrating that equipment and reagents are validated for use in reproductive SoHO and do not pose harmful effects to recipients;
- Verify that staff are adequately trained and competent for all critical tasks;
- Confirm that technologies and validated systems are in place to minimise the risk of human error throughout SoHO handling and application;
- Validate compliance with national legislation regarding limits to the number of offspring from MAR, monitored through donor registries.
- Validate compliance with national limits to the number of offspring from MAR donors, in case of cross border distribution.

Reporting of Serious Adverse Events and Reactions

All Serious Adverse Events (SAE) and Serious Adverse Reactions (SAR) associated with the donation, processing, storage, distribution, or clinical application of SoHO must be reported without undue delay and in accordance with reporting requirements.

This obligation applies to:

- Third-party donors who experience reactions such as ovarian hyperstimulation syndrome (OHSS), infection, or other clinically significant complications;
- Recipients, where any adverse reaction or unexpected clinical outcome may be linked to the quality or safety of SoHO (*e.g.* infection, immunological reaction, or toxic exposure);
- Offspring from MAR procedures, where relevant adverse outcomes may be associated with the applied SoHO or reproductive materials.

The inspection focus should be on:

- Verify that a vigilance system is established and functional;
- Confirm that all SAE/SAR are detected, documented, and reported within required timelines;
- Review traceability and follow-up documentation linking donor, recipient, and offspring;
- Ensure that CAPAs are implemented and reviewed for effectiveness;
- Verify that information from a distributing sperm bank on blockage of donors is followed up appropriately (donor immediately blocked, impact on recipients and offspring evaluated and, where relevant, reported as a SARE and communicated).

Traceability and Data Systems

All reproductive SoHO shall be traceable from donor to recipient and offspring, and vice versa, throughout collection, processing, storage, distribution, and clinical application.

The inspection focus should be on:

- Verify the presence and functionality of a validated traceability system covering donors, recipients, and offspring;
- Confirm that donor–recipient–offspring identifiers are unique, secure, and confidential;
- Confirm cross-border traceability procedures (SEC coding).

Performing inspection on site

Onsite inspections enable the direct review and examination of documentation, facilities, equipment, and clinical activity to verify compliance with the SoHO Regulation (EU) 2024/1938. Inspections shall be conducted in a manner that respects the continuity of clinical operations, protects patient and donor confidentiality, and provides constructive, educational feedback to the inspected establishment.

During inspections, competent authorities shall verify that all regulatory, clinical, and operational requirements are in place and effectively implemented. Inspectors shall confirm that:

- Authorisations: All applicable authorisations (SoHO entity, SoHO establishment, and/or SoHO preparation are valid, current, and correspond to the activities performed.
- Procedural compliance: Critical procedures, approvals, and quality safeguards are implemented to ensure compliance with the applicable quality, safety, and traceability requirements.
- Clinical documentation: Clinical records are complete and accurate, including testing documentation, ethnic background, and genetic-risk evaluations where relevant.
- Counselling and consent: Counselling is properly documented, demonstrating that donors and recipients were fully informed of procedural risks such as ovarian hyperstimulation syndrome (OHSS), sedation, oocyte retrieval risks, and potential emotional outcomes for both donors and beneficiaries.
- Standard Operating Procedures (SOPs): SOPs are established and current for every critical step, ensuring correct identification and traceability to prevent misidentification or mix-up errors in the allocation of gametes or embryos.
    - The use of false identification documents constitutes fraudulent activity;
    - The four-eye principle (dual witnessing) or validated electronic witnessing systems shall be applied at all critical steps;
    - Mix-ups are considered never events and must be immediately investigated;
    - All mix-up incidents, regardless of whether SoHO are applied to the recipient, must be investigated immediately. Where the incident meets the criteria for a SAE, it shall be reported to the competent authority in accordance with the Regulation.
- Traceability: Dates and staff participating at each successive step are fully documented, recognising that MAR procedures involve multiple operators. Traceability shall extend to all medical devices, consumables and culture media used. Materials should be devoid of any toxicity towards reproductive tissues, gametes and embryos, and embryo tested consumables are recommended.
- Personnel: Staffing levels are adequate for the annual volume and complexity of MAR procedures, and personnel are appropriately trained and competent.

- Equipment: Equipment is suitable for the workload, with documented maintenance and calibration.
    - The number of incubators shall be sufficient to minimise door opening and maintain stable culture conditions;
    - Remote alarm systems for critical equipment are advisable.
- Laboratory environment: Air quality complies with HEPA and VOC control standards. Both background and processing air quality shall meet with European and national guidelines and be regularly monitored.
- MAR procedures: Inspectors shall verify compliance with national legal provisions governing eligibility for MAR, including age limits, genetic assessment policies to the extent that National law allows for genetic testing, anonymity and donor-identifiability rules, surrogacy restrictions, and post-mortem use regulations.
- Confidentiality and records: All processes uphold confidentiality standards, and patient follow-up data are accurately recorded and securely stored.

Annex 7: Inspection of medical devices and in vitro diagnostics medical devices in SoHO entities

References

- Regulation (EU) 2017/745 on medical devices.
- Regulation (EU) 2017/746 on in vitro diagnostic medical devices.
- Regulation (EU) 2019/1020 on market surveillance and compliance of products.

A medical device is an instrument, apparatus, device, software, implant, reagent, material or other object intended to fulfil a specific medical purpose, the principal intended effect of which is achieved in or on the human body and is not achieved by pharmacological, immunological, or metabolic means.

For medical devices (MDs) and in vitro diagnostic medical devices (IVDs), detailed legal provisions exist at European level (Regulation on medical devices and Regulation on in vitro diagnostic medical devices). However, detailed knowledge of these regulations is not required for inspectors in the SoHO sector.

Notified bodies assess medical devices to ensure they meet safety, performance, and quality requirements before they can be placed on the European market and bear the CE mark. In each Member State, a competent authority is responsible for market surveillance of MDs/IVDs. These authorities perform checks to ensure that devices placed on the market comply with EU legislation. SoHO inspectors should interact with this authority if there is suspicion of a safety issue or unlawful MD/IVD use.

MDs/IVDs used within a specific establishment can be identified in the Preparation Process Dossier.

The task of the SoHO inspector is to obtain an overview of the MDs/IVDs used within a SoHO establishment. It is necessary to identify which MDs/IVDs are in use and whether they are CE marked. MDs/IVDs that are not CE marked should be subject to closer examination, either by a SoHO inspector, an MD/IVD specialist, or through a combined approach. These may pose a higher risk and could be non-compliant with applicable legislation. Inspectors should apply a risk-based approach and follow risk signals. It is important to recognise that in-house MDs/IVDs are not CE marked and must be validated by the establishment using them. The Preparation Process Authorisation (PPA) process should also cover the validation of MDs/IVDs used.

This approach should avoid duplication of conformity assessments already performed under applicable MD/IVD legislation and should instead focus on the use of the device within the SoHO process and its impact on quality and safety.

For CE-marked MDs/IVDs, it is important that the device has a manufacturer responsible for the CE marking, who defines the intended purpose of the device. Inspectors should verify that the MD/IVD is used in accordance with this intended purpose.

A clear distinction should be made between CE-marked devices and in-house or off-label use of MDs/IVDs. For CE-marked devices, inspection should focus on their use within the SoHO process and compliance with the intended purpose as defined by the manufacturer. For in-house devices or use outside the intended purpose, the establishment should ensure appropriate justification, a documented risk-based assessment, and validation within its Quality Management System (QMS).

The assessment of whether an MD/IVD is used in accordance with its intended purpose may require specific clinical or technical expertise. Where such expertise is not available, the SoHO inspector should not independently assess the clinical appropriateness of use but should verify that the intended purpose is clearly defined, documented, and consistently applied within the establishment. Where necessary, support from specialised assessors (e.g. MD/IVD experts or clinical specialists) should be sought.

If an MD/IVD is used outside its intended purpose, the responsibility of the manufacturer no longer applies, and the establishment effectively assumes the role of manufacturer. The establishment is therefore responsible for the legal conformity of the device. This represents a higher-risk situation and should be discussed with the competent authority responsible for market surveillance of MDs/IVDs.

The following legal concepts are essential for understanding medical device legislation:

- The manufacturer is the natural or legal person responsible for placing a medical device (MD) on the market;
- The manufacturer must ensure that the medical device complies with applicable legal requirements;
- The user must use the device in accordance with its intended purpose, as specified by the manufacturer.

MDs/IVDs are subject to operational requirements that must be followed in accordance with the manufacturer's instructions. Only under these conditions can an MD/IVD be considered appropriately qualified and validated for use.

The inspector should therefore verify whether the user:

- Operates the MD/IVD in accordance with the manufacturer's intended purpose, or, where this is not the case, ensures that its use within the establishment is appropriately justified and validated;
- Has appropriately qualified and/or validated the device;
- Maintains the device in accordance with the manufacturer's requirements;
- Uses suitable and compatible equipment and materials (*e.g.* Appropriate reagents).

The inspector's task is to verify that the SoHO establishment follows the manufacturer's instructions for use of the MD/IVD.

Performing inspection on site

According to Regulation 2017/745 Article 2 (39) 'reprocessing' means a process carried out on a used device to allow its safe reuse including cleaning, disinfection, sterilisation and related

procedures, as well as testing and restoring the technical and functional safety of the used device.

MDs/IVDs must be reprocessed in accordance with the manufacturer's instructions. Otherwise, it cannot be assumed that a MD/IVD can meet for example the necessary hygiene requirements. If an entity deviates from the manufacturer's instructions during reprocessing, it becomes the manufacturer of the reprocessed MD/IVD. An increased risk can be assumed. The inspector should pay attention to reprocessing.

In-house medical devices

MDs/IVDs that are not industrially manufactured and therefore do not bear the CE mark may only be manufactured as in-house products in healthcare entities.

The reason could be that there is no suitable MD/IVD on the market and therefore the establishment produces its own (non-industrial in-house products).

Due to the complexity of the legal situation, the SoHO inspector should contact the competent market surveillance authority and consult a relevant MD inspector. It is essential that the risk situation and the legality of such MDs/IVDs is assessed in a joint surveillance measure (SoHO and MD/IVD Market Surveillance). However, the inspector can at least clarify why such MD/IVD, that is not CE marked, is in use and ask the entity about it.

In any case, at the end of the inspection, the SoHO authority should know whether:

- Such a MD/IVD is lawful;
- It poses a risk that can be accepted or that cannot be accepted.

If possible, risks should be clarified during the inspection and should not be transferred to other authorities in a referral and open-ended manner.

SoHO entities that are not within registered healthcare entities (hospital) are not allowed to manufacture MDs/IVDs in-house. It is important for the inspector to know whether a SoHO entity is within a registered health entity or not. This must be clarified in cooperation with the Market Surveillance Authority for MDs/IVDs who is responsible for interpreting medical device law in this context.

Annex 8: Inspection of Computerised Systems in SoHO Entities

References

- SoHO entities may store data in electronic form to ensure traceability (art 42.6)
- When carrying out SoHO activities, SoHO entities must, to the extent possible, make use of technologies that reduce the risk of human error (art. 58.11).

When inspecting SoHO entities, inspectors will most likely come across computerised systems. When carrying out SoHO activities, SoHO entities shall, to the extent possible, make use of technologies that reduce the risk of human error (article 58.11). Computerised Systems (CS) shall be validated and maintained in a secure state during all process steps where applicable. The inherent complexity of computerised systems requires a detailed knowledge of IT.

In the ideal situation, CS are evaluated by specialised assessors. Preparing for a general inspection, a SoHO inspector could contact an assessor at the Competent Authority (CA) to investigate what general items should be observed during inspection according to a risk-based approach covering those functionalities that may have an impact on the safety of the donors, patients, products or offspring. The onsite observation will verify these CS functionalities in its routine application.

If no specialised assessors are available at a Competent Authority, an inspector can use this annex during an inspection. The depth of the inspection performed by an inspector, who is not a specialised assessor, will depend on his/her knowledge and qualification. This annex aims to give a general overview. For more in-depth information, EudraLex - Volume 4 - Good Manufacturing Practice (GMP) guidelines Annex 11 and the chapter on Computerised Systems in the EDQM guide for the quality and safety of tissues and cells for human application on computer validation could be of help.

CS is a set of software and hardware components which together fulfil certain functionalities. Computerised systems should be integrated within the organisation's Quality Management System (QMS). The application should be validated, including documentation of the verification of pre-defined user requirements. The relevant IT infrastructure, including operators, should be qualified

Where a CS replaces a manual operation, product quality, process control or quality assurance shall not be weakened. The overall risk of the process shall remain unchanged or even improved by eliminating potential operator failures.

A traceability system is required for essentially all procedural steps, *e.g.* from donor recruitment to the SoHO application at the patient preferably extended to the follow up and surveillance (article 42). If this is a digital system, it should be validated and this validation could be reviewed during inspection.

This guidance does not provide an in-depth assessment of computerised systems but is intended to support inspectors in identifying key aspects during routine inspections.

Practical guidance for the inspection of computerised systems with onsite verifiable items which can be documented for the computerised systems' specialist at the CA. This is a non-exhaustive list.

Generically, the following approach is recommended:

Before or during inspection, the following topics could be requested from the SoHO entity:

- The validation system and the principal approach of the entity to the validation of the CS shall be described in a high-level document;
- The validation system for CS shall be firmly rooted in the quality assurance system of the entity;
- The scaling of the CS's validation must be based on a risk-based approach;
- The roles and responsibilities:
    - In the validation system for CS;
    - In the validation projects for CS; and
    - The associated personnel qualification shall be defined; this should include level of access and defined responsibilities.
- As part of a risk management system, decisions on the extent of validation and data integrity controls should be based on a justified and documented risk assessment of the computerised system. This includes regular updates and upgrades of IT systems (software and/or hardware), which shall be performed in a controlled manner, including appropriate change control, validation, and documentation. Computerised systems shall ensure data integrity in accordance with ALCOA+ principles (Attributable, Legible, Contemporaneous, Original, Accurate), and compliance with these principles should be verified during inspections.
- The entity shall clearly present to the inspector
    - Whether all CS in the entity have been identified;
    - What their validation status is; and
    - Whether there is a corresponding validation report for each CS.

The following questions are intended as practical, non-exhaustive prompts to support inspection and do not replace a comprehensive, risk-based assessment of computerised systems, including data integrity, security, and business continuity requirements. During inspection, the inspector should verify the following:

1. Has each operator its own personal password (and personal level of access), to enable tracing of each login and modification?
2. Does the operator put the screen to sleep before he/she departs from the computer/laptop (observe carefully during inspection)?
3. Is data back-up and safe data protection ensured for a long period (*e.g.* readable after 30 years, mirroring hard disks, external storage of hard disks – is it in the same facility, cloud storage)?

4. Is there a documented disaster recovery plan in place, including an alternative system or contingency process to ensure continuity in case of system failure?
5. If any aspect of CS (*e.g.* installation, maintenance) is provided by a third party, there should be an agreement in place which clearly outlines responsibilities. This should detail any remote access by the third party that may be required.
6. Are all critical data recorded, *e.g.* personnel, witness, the intended end-user and/or patient of every SoHO, any materials or equipment that have come into contact with those SoHO that might pose a risk to their quality or safety in each step of the process (check with real data)?
7. Is tracing of SoHOs from donor to recipient and vice versa possible with the CS (this could be different systems)?
8. Do SOPs at the workplace of the operator describe how a SoHO is identified in each step?
9. Are double checks mandatory when entering data manually into the CS, *e.g.* the process must be verified and recorded by the operator?
10. Is electronic witnessing established *e.g.* Radio Frequency Identification labels - RFID Tags & Reader, Barcodes?
11. What is the back-up plan in case of system failure?

Annex 9: Risk-based inspection planning of SoHO establishments (already adopted)

Annex 10: Risk-based inspection planning of SoHO entities, third parties, and third country suppliers (already adopted)

Annex 11: Proposed Format for a SoHO Establishment Dossier (SED) (writing in progress)

Annex 12: Proposed Format for a SoHO Importing Establishment Dossier (SIED) (writing in progress)

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