EUROPEAN COMMISSION
HEALTH AND FOOD SAFETY DIRECTORATE-GENERAL

Directorate D - Health systems and products
D4 – Substances of Human Origin and Tobacco Control

INSPECTION OF TISSUE AND CELL PROCUREMENT AND TISSUE ESTABLISHMENTS

Operational Manual for Competent Authorities

Version 1.1

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This Operational Manual for Competent Authorities has been established for information purposes only. It has not been adopted or in any way approved by the European Commission. It is not legally binding.

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1.0 Introduction

Article 7 of Directive 2004/23/EC[1] establishes the need for inspections and control measures. Paragraph 5 provides that 'Guidelines concerning the conditions of the inspections and control measures, and on the training and qualification of the officials involved in order to reach a consistent level of competence and performance, shall be established in accordance' with the *Comitology* procedure.

This Operational Manual aims to support EU Member States (MS) with implementing a series of regulatory tasks to comply with Directives 2004/23/EC, 2006/17/EC[2], 2006/86/EC[3] and (EU) 2015/566[4]. It covers:

- inspection, accreditation, designation, authorisation or licensing of tissue establishments (TEs)
- inspection and authorisation of the conditions for tissue and cell procurement;
- inspection and authorisation of preparation processes for tissues and cells;
- inspection and authorisation of importing tissue establishments (ITEs), inspection of third country suppliers (3CS) and export activities.

The Operational Manual is intended to support MS that are establishing such regulatory systems for the first time. It should also promote standardisation of regulatory systems that are already well established in the European Union.

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1 Directive 2004/23/EC of the European Parliament and of the Council of 31 March 2004 on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells (OJ L 102, 7.4.2008, p. 48).

2 Commission Directive 2006/17/EC of 8 February 2006 implementing Directive 2004/23/EC of the European Parliament and of the Council as regards certain technical requirements for the donation, procurement and testing of human tissues and cells (OJ L 38, 9.2.2006, p. 40).

3 Commission Directive 2006/86/EC of 24 October 2006 implementing Directive 2004/23/EC of the European Parliament and of the Council as regards traceability requirements, notification of serious adverse reactions and events and certain technical requirements for the coding, processing, preservation, storage and distribution of human tissues and cells (OJ L 294, 25.10.2006, p. 32).

4 Commission Directive (EU) 2015/566 of 8 April 2015 implementing Directive 2004/23/EC as regards the procedures for verifying the equivalent standards of quality and safety of imported tissues and cells (OJ L 93, 9.4.2015, p.56)

The scope of this Operational Manual reflects these related Directives on the quality and safety of human tissues and cells used for transplantation or in assisted conception.

Sections of this Manual are relevant for human tissues and cells used, for example, as a starting material for manufacturing advanced therapy medicinal products (ATMPs) (i.e. for gene therapy, somatic cell therapy or tissue engineering). In these cases the regulatory requirements laid down by the above-mentioned Directives for donation, procurement and testing apply. Regulation 1394/2007 on advanced therapy medicinal products[5] applies with effect from 30 December 2008. MS are advised to prepare an integrated system to manage their regulatory responsibilities at the interface between the tissues/ cells and medicinal sectors (i.e. site status, inspection practices, accreditation, designation, authorisation or licensing process, traceability of materials and coding systems).

2.0 Responsibilities of the inspectors

Inspectors should be given a clear mandate, in writing, by the competent authority for the specific task and should be issued with an official means of identification. They should gather detailed information to be provided to the competent authority in line with the specific mandate for the inspection.

An inspection is a sampling exercise, as inspectors cannot examine all areas and documentation during a single inspection. Inspectors are not responsible for any deficiencies that could not be detected during the inspection because of limited time or scope or because certain processes could not be observed during the inspection.

3.0 Qualifications and training

3.1 Education and experience

Inspectors should at least:

[5] Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004 (OJ L 324, 10.12.2007, p. 121).

(a) possess a diploma, certificate or other evidence of formal qualifications in medical or biological sciences, awarded on completion of a university course or a course recognised as equivalent by the Member State concerned;

and

(b) have practical experience in the relevant areas within a tissue, cell or blood establishment. Other prior experience may also be counted as relevant.

In exceptional cases, the competent authorities may consider that a person's considerable relevant experience may exempt him or her from requirement (a).

Inspectors should have practical post-graduate experience in relevant areas within a tissue, cell or blood establishment. Other prior experience which may also be considered relevant includes: appropriate experience in the pharmaceutical industry; healthcare experience; or regulatory experience of working within a competent authority (CA) that inspects blood establishments or hospital blood banks, tissue and cell establishments or medicinal products.

3.2 Personal qualities

Inspectors should possess good interpersonal skills. They should be good communicators, be able to discuss and debate effectively, display a quick grasp of complicated issues and act assertively, while maintaining an appropriate level of tact and professional behaviour.

Inspectors should have a high level of personal integrity and maturity, be open-minded, understand complex issues, possess sound judgment, assertiveness, analytical skills and tenacity and have the ability to perceive situations in a realistic way.

3.3 Induction training

In order to obtain a position within an Inspectorate, new inspectors will have demonstrated that they possess the qualifications and/or experience necessary to perform the functions expected of them. In addition, it must be recognised that the skills required of an inspector are specialised. Induction training will therefore be provided by the Inspectorate, regardless of qualifications or previous experience.

Induction training should cover at least the following topics:

- TE activities (donation, procurement, testing, processing, preservation, storage and distribution);
- Accreditation, designation, authorisation or licensing systems in the MS;
- EU Directives on tissues and cells;
- Inspection techniques and procedures, including practical exercises;
- International quality management systems (ISO and EN);
- National health systems and tissues and cells organisation in the MS;
- National legislation in place in the MS;
- Organisation of national regulatory authorities;
- International inspection instruments and other relevant bodies.

Inspectors should also receive continuous training on the above-mentioned topics to keep up with any technical and legal changes.

3.4 Specialised training

As stated above, inspectors will, in general, have a wide range of skills obtained from their education, qualifications, previous work experience and/or additional training. However, inspectors are unlikely to have the same level of knowledge in every subject relating to tissues and cells. A procedure should be in place to perform a training needs analysis for new employees and current staff to ensure that inspectors can perform inspections to the required standard.

Important subjects in which inspectors may require specialised training include:

- General principles of transplantation of tissues and cells;
- Basic knowledge of processes and equipment used in TEs;
- Basic principles of medically assisted reproduction techniques (MART);
- Basic knowledge of regulations applicable to medical devices;
- Basic knowledge of pharmaceutical legislation (in particular, of the ATMP Regulation);
- Design, validation and maintenance of critical environments and equipment;
- Data processing and protection systems;
- Effective communication, including conflict management;
- General hygiene;
- Identification of, and subsequent action against, illegal or fraudulent activity;
- Laboratory techniques, *in vitro* diagnostic tests (screening tests and nucleic acid amplification techniques);
- Risk management;
- Specific national guidelines/requirements;
- Transmissible diseases;
- Vigilance and surveillance.

Inspectors should also receive continuous training on the above-mentioned topics to keep up with any technical and legal changes.

3.5 In-service training

The in-service training programme should include a number (to be defined by the Inspectorate) of witnessed inspections. Trainee inspectors should first observe an authorised inspector performing a number of inspections, then participate in a number of inspections themselves and, finally, lead a number of inspections under the supervision of an authorised inspector.

3.6 Authorisation

The competence of the trainees must be confirmed and documented by the CA before they are authorised to lead inspections.

Inspectors' performance and competence should be periodically reviewed in the light of the requirements of the quality system applied by the competent authority/Inspectorate.

4.0 Types of inspection

Different types of inspection may be carried out, depending on the activities of the TE and third parties involved. They can be on-site or desk-based. They can cover the entire system or focus on one or more specific themes (quality systems, processing of specific tissues or cells, specific preparation process or a particular problem, etc.).

General system-oriented inspections should be conducted on-site and cover all processes and activities, including organisational structure, policies, responsibilities, quality management, personnel, documentation, facilities, equipment, contracts, complaints, recalls, audits, etc.

- They should be carried out at least once every four years of activity.
- They should be carried out before a TE is accredited, designated, authorised or licensed. (However, accreditation/designation/authorisation/licensing might need to be based on a document review.)
- They could be necessary for any significant variation from the initial accreditation, designation, authorisation or licensing (e.g. change in the activity or in the preparation processes).
- They could also be necessary if there is a history of deficiencies (e.g. serious adverse events (SAE) or serious adverse reactions (SAR)).

Thematic inspections should be conducted on-site and cover one or more specific themes, such as quality management systems, processing of specific tissues or cells, specific preparation processes, etc.

They need to be conducted:

- At the time of an intermediate evaluation, in between two general system-oriented inspections;
- When preparation processes are new, complex, innovative or unique to a TE;
- Whenever a significant change is reported in one of the specific themes;
- When necessary, if there is a (history of) specific deficiency (e.g. SAE or SAR) .
- When a TE starts to import T&C from third countries.

Desk-based reviews do not take place on-site, but at a remote location. They can cover all processes and activities or focus on one or more specific themes. They will be based on an up-to-date tissue establishment dossier (TED). They could be used in the following situations:

- To perform an initial assessment of the TE activities;
- In preparation for on-site inspections;
- At the time of an intermediate evaluation, in between general system-oriented inspections, if there have been no significant changes.

Re-inspections may be necessary as a follow-up or re-assessment to monitor the corrective action required in response to the previous inspection.

Other specific inspections may also be conducted:

Inspections of donor-testing laboratories: On-site assessment of compliance with good quality-control laboratory practice normally forms part of these inspections. They may be performed by a CA other than the CA responsible for TE inspection, depending on the situation in each MS. However, they could be part of a general system-oriented inspection or of a thematic inspection if the testing laboratory is part of a tissue establishment.

Inspections of third-parties: Competent authorities should perform on-site inspections of third parties, in particular where a risk assessment indicates that it is appropriate. Inspections of third parties should be considered in the following situations, for example:

- Where third parties act as suppliers of critical services to a significant number of TEs, e.g. a commercial tissue-processing facility, a centralised tissue donor-selection and/or procurement organisation or a contracted sterilising company.
- Where third parties act as suppliers of critical services to a single TE, but that establishment supplies a large volume of tissues or cells.
- Where inspection of the TE indicates a high level of non-compliance with the written agreement by a third party.

Joint inspections: Specific circumstances, including limited resources or expertise, could lead a Member State to consider requesting another EU competent authority to carry out joint inspections on its territory in collaboration with officials from the requesting Member State.

5.0 Inspection scheduling

CAs should plan the sequence of inspections in advance. They should draw up a programme and ensure that the frequency of inspection of individual TEs can be adhered to as planned. Sufficient resources should be made available to carry out the designated programme of inspections in an appropriate manner.

Directive 2004/23/EC requires that tissue establishments be inspected at least at two-yearly intervals. It recommends that a general system-oriented inspection covering all areas of activity should be performed at least every four years. During the interval between two general system-oriented inspections, a thematic inspection may be performed which focuses on a particular theme or process (perhaps related to previously reported deficiencies or new activities). Alternatively, if there have been no significant changes since the last on-site inspection, a desk-based review may be performed.

5.1 Prioritisation of inspections

Inspections should be scheduled in accordance with documented criteria based on risk assessment. For routine inspections, scheduling criteria should be linked to the following indicators:

- Complexity of site operations;
- Compliance with existing regulations (as indicated in the completed TED);
- Evidence of past performance (e.g. number of deficiencies detected in a previous inspection);
- Number of adverse events/reactions reported or recalls ordered;
- Volume of activity, including significant changes.

5.2 Unannounced inspections

Inspections may be organised without giving notice to the TE, where there is evidence or information to justify such action. The criteria for conducting such unannounced inspections could include suspicion of illegal or fraudulent activity, serious breaches of legal requirements which might expose donors or recipients to risk, a serious adverse reaction resulting in patient death or a major product recall, etc.

6.0 Inspection procedures

This section gives general guidance on the procedures for any type of inspection. Annexes 1 to 5 provide technical guidance on how to verify compliance with the specific technical requirements for: tissue and cell procurement and donor testing (Annex 1); reception, processing, storage and distribution (Annex 2); assessment of preparation processes (Annex 3); evaluation of risk assessment reports (Annex 4) and import/export (Annex 5).

6.1 Inspection procedures — Before the inspection

The membership of the team should be decided, taking into consideration the type of inspection.

A single inspector may conduct the inspections if risk assessments performed by the competent authorities prior to inspection have identified the TE as suitable for a single person to inspect. In general, however, inspections by a single inspector should be avoided.

Resources permitting, the team should be made up of members with different expertise. At least one of the inspectors should have the level of competence/education required by Article 17 of Directive 2004/23/EC for the responsible person for the TE or have the education and training necessary in order to be able to inspect the site.

When necessary, inspectors may request the assistance of a technical expert (e.g. in stem-cell technology or medically assisted reproductive technology) or of other (e.g. legal or medical) experts for a specific inspection. The experts should have specialist knowledge in the field covered by the inspection. The role of experts is not to inspect but to advise

the inspectors on technical matters. The role of the experts in the team should be clearly defined in formal documents, the confidentiality agreement signed by the experts and their declaration of no conflict of interest. Experts should be informed of the Inspectorate's policy on conducting inspections.

Before conducting the inspection, the team should familiarise itself with the organisation to be inspected. This should include at least:

- Examination of the tissue establishment dossier (TED) to review the current status with respect to the EU Directives on tissues and cells and any relevant national regulations;
- Examination of the preparation process dossier (PPD);
- A review of the reports from previous inspections, if any;
- A review of variations (changes) to the TE authorisation, if any;
- Any specific clothing/vaccination requirements for entry to the TE;
- A review of the follow-up action (if any) in response to previous inspections;
- A review of tissue or cell recalls initiated since the previous inspection, if any;
- An examination of relevant serious adverse events (SAE) or serious adverse reactions (SAR) notified since the previous inspection, if any;
- A review of any national standards or guidelines applicable to the site to be inspected;
- Volume of activity, including significant changes.

An inspection plan may be prepared specifically for the inspection to be performed. It should address any issues arising from the pre-inspection review that require specific investigation during the inspection and highlight any relevant issue noticed during examination of the TED to make sure that it is discussed and assessed during the inspection.

It is recommended practice to inform the organisation to be inspected, in advance, of:

- The objectives and scope of the inspection, in the light of previous inspections, including inspection of procurement establishments where relevant;
- The people whose presence is required during the inspection; in cases where particular processes are to be inspected, the people directly responsible for them should be present;
- The identity of the members of the inspection team and their individual roles;
- When and where the inspection is to be conducted (date, time and place);
- The organisational units to be inspected;
- The estimated time and duration for each major inspection activity (premises, processes, etc.);
- An outline of the main documentation that should be available for review during the inspection.
- The schedule for the opening and final meetings;
- The approximate schedule for transmission of the written inspection report;
- The possibility that, where relevant, the results of the inspection may be shared with other regulators in the same or another CA.

6.2 Inspection procedures — During the inspection

Inspectors should strive to create a constructive atmosphere during the inspection. They should be aware of their influence over decision-making processes. They should answer questions but avoid taking on the role of a consultant. However, the inspectors' tasks are not limited exclusively to detecting faults, deficiencies and discrepancies; they should accompany any findings with instructive and motivating comments.

Inspections could disturb normal work patterns in the organisation inspected. Inspectors should therefore take care not to put the tissues or cells at risk and should work in a careful, planned way.

Inspectors will have access to confidential information. They must handle it with integrity and great care and in compliance with the legal requirements for protection of confidentiality and for disclosure with a view to protection of public health.

In some cases, inspectors may take copies of documents that might be useful for drafting the initial inspection report or as evidence of particular findings. In some MS, inspectors are allowed to take photographs or videos for evidence at the sites, as long as they do not interfere with the process or with the quality and safety of the tissues or cells.

6.2.1 Opening meeting

Inspections should begin with an opening meeting at which the inspection team should normally meet the management and the key personnel of the organisation, including the responsible person (RP). The purpose of this meeting is to introduce the team and any accompanying official(s) or specialist(s) and to discuss the inspection plan (which may be subject to unannounced changes).

During the opening meeting the inspection team should:

- Outline the purpose and scope of the inspection;
- Review the management structure of the organisation (organisation chart);
- Although all documents should be available at this stage, identify documents which may be required during the inspection, depending on the activities/areas on which the inspectors choose to focus;
- Confirm that all information will be treated as confidential;
- Explain whether deficiencies will be notified as they are identified or at meetings at the end of each day to sum up the results or not until the final closing meeting.

Upon request, the TE team should be able to:

- Describe the quality management system;
- Explain the organisational structure and operating procedures;
- Explain each step from procurement to processing and distribution;
- Explain significant changes in facilities, equipment, processes and personnel since the last inspection;
- Explain how deficiencies have been resolved if this information has not already been forwarded to the CA;
- Designate the people to accompany the inspection team during the inspection;
- Allocate a room for the inspectors, if needed; if the inspection is conducted by a team, a separate room will be required for the team's debriefing.

A quick tour of the site immediately after the opening meeting could be valuable for familiarisation with the site and any significant changes since the previous inspection.

This should not replace the detailed tour of the facilities later in the inspection. In some instances, it might be necessary at this stage to observe certain activities that will not be taking place when the area is visited later in the inspection.

6.2.2 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, as described in the TED, and whether the way in which they are used suits the intended operations. Any changes since the last inspection should be reviewed. Normally, inspectors follow the process flow of the activities for which the TE is or will be authorised, taking into account the detailed provisions of Directives 2004/23/EC, 2006/17/EC and 2006/86/EC. Sometimes it is appropriate to concentrate on one department of the organisation if there are special problems or requirements. Relevant service areas should be considered, e.g. water, steam or ventilation systems and engineering support.

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

6.2.3 Review of documentation

The documentation system, including specifications, preparation processes, transport and packaging instructions, procedures and records covering the different processes, quality control and distribution operations should be checked by examining selected examples, both during use and after compilation into complete records.

A general system-oriented inspection will normally include examination of the documented quality management system for the activities for which authorisation has been granted or is sought, including the following indicative list:

- Job descriptions, organisation chart, role of the RP and the nominated medical practitioner[6];
- Training of staff, including initial/induction training, retraining plans and competence assessment;
- Document control, including maintenance (e.g. change control) of standard operating procedures (SOPs);
- Validation (processes) and qualification (equipment and facilities);
- Preventive maintenance programmes (equipment and facilities);
- Tracking and trending of sterility testing and air quality conditions;
- Selection criteria for suppliers, if relevant;
- Third-party and supplier contracting;
- 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;

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[6] Every tissue establishment must have access to a nominated medical practitioner to advise on and oversee the establishment's medical activities, such as donor selection, review of clinical outcomes of applied tissues and cells or interaction, as appropriate, with clinical users.

- Management of complaints, non-compliance, serious adverse reactions (SAR), serious adverse events (SAE), recalls and contingency plans for termination of activities;
- Traceability, data handling and confidentiality;
- Import/export;
- Record-keeping: annual report on activities and annual report on vigilance.

The responsible person should be interviewed and a critical assessment should be made of his or her role.

Operations contracted out and the responsibilities of the different parties should be clearly identified. Contracts should be examined for compliance with the national regulations transposing Directives 2004/23/EC, 2006/17/EC and 2006/86/EC.

The procedure for recording and reviewing SAE and SAR and the system for recalling distributed tissues and cells from within and outside the MS should be examined during the inspection. Any reports of SAR and SAE should be examined and discussed.

The system for performing self-inspections in the organisation should be examined. Although the reports themselves would not normally be read by the inspectors, a review of the audit/self-inspection schedule for the previous year can be useful to confirm satisfactory completion of audits. This can be followed up by checking the log of corrective and preventive action at the times that audits/self-inspections were performed to ensure that appropriate action has been taken.

Procedures for controlling tissue and cell imports or exports (where relevant) should be reviewed and documentation relating to individual cases should be examined. Technical guidance on inspection of imports and exports is given in Annex 5.

Thematic inspections will include examination of the documentation related to the theme in question.

In the case of process-related inspections, this will include the specific documentation relating to one or more completed or uncompleted processes for preparation of specified tissues or cells, including:

- Compliance with the preparation process dossier (see Annex 9);
- Traceability and tracking (including the donor and tissue/cell coding system in place);
- Process validation;
- Processing instructions (SOPs) and records;
- Release procedures;
- Specifications and quality control data for starting materials, intermediates and finished tissues and cells, other materials, reagents and technical devices;
- Packaging and labelling;
- Distribution.

6.2.4 Final meeting

Once the inspection has been completed, inspectors should sum up the findings in the final meeting with representatives of the organisation, normally the RP, the person in charge of the quality management system (where relevant) and any staff invited by the RP. The final meeting is a significant part of the inspection. The deficiencies observed during the inspection should be described clearly and, if required by the CA's SOP, notified to the organisation in writing. A proposed standard format is shown in Annex 7. Verbal indication should be given of the seriousness of the deficiencies noted. Facts and objective evidence supporting the observations, particularly regarding major or critical findings, should be described during this meeting. The organisation may, if it wishes, discuss initial proposals for remedial action. As far as possible, all relevant observations should be reported at this meeting, so that the organisation can initiate the necessary corrective action as soon as possible. Deficiencies should be reported with reference to the national laws transposing the three EU Directives on tissues and cells. In the case of critical deficiencies posing an immediate risk to the health and safety of donors and recipients of tissues and cells, the Inspectorate should delegate powers to the inspectors to request immediate quarantine and/or cessation of supply and, where relevant, recall of the human tissues or cells involved. The relevant CA's SOPs must be followed in such special circumstances.

6.2.5 Inspection notes

Inspection reports should be based on notes taken during the inspection. These notes should be managed in accordance with the practices specified by the CA. An inspection findings form which could be used to record the findings is provided in Annex 7.

6.3 Inspection procedures — After the inspection

6.3.1 Inspection report and corrective action

A written inspection report should contain general information on the TE, a description of the inspection and the observations and conclusions arising from it. The report should also contain a reference to the tissue establishment dossier (TED), together with any corrections to the TED noted from the inspection.

A proposed standard format for the report is shown in Annex 8. It includes a standard classification of deficiencies. Either the inspection findings may be extracted from this report and sent to the TE in a letter or the entire report may be sent to the TE, depending on the CA's internal procedures.

The conclusions of the report should clearly identify deficiencies, classifying them as critical, major or other (based on the definitions given in Annex 8). This is usually done at the Inspectorate to ensure consistency with other inspections. A date should be set by which the TE should submit proposals and a schedule for rectifying the deficiencies outlined in the report (action plan). The inspectors should evaluate the proposed action plan and, on that basis, make a recommendation to the authorising CA in line with the specific mandate of the inspection, clearly stating whether or not the TE complies with the national laws transposing Directives 2004/23/EC, 2006/17/EC and 2006/86/EC.

The TE should be informed of the decision in writing.

In some cases, the inspection team may consider it necessary to conduct a second site visit (re-inspection) or to request additional information on corrective action before making a recommendation. The action taken by the CA will depend on the nature and extent of any deficiencies and the adequacy of the corrective action plan, in the light of

the EU Directives and the CA's broad knowledge of existing practices relating to all types of TE.

6.3.2 Accreditation, designation, authorisation or licensing of TEs

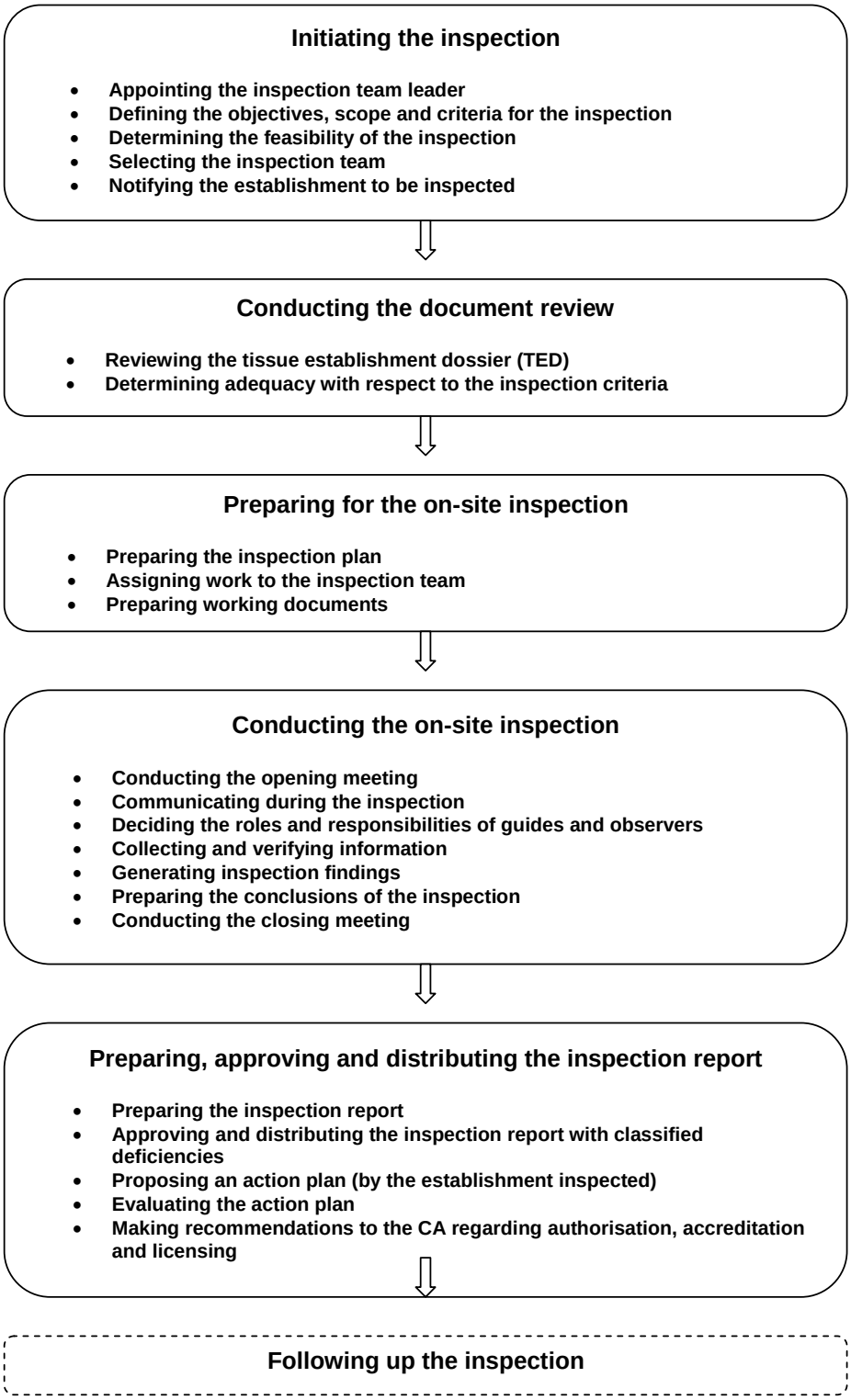
In accordance with Article 6 of Directive 2004/23/EC, tissue establishments must be accredited, designated, authorised or licensed by a CA for the activities they carry out.

A format for an authorisation certificate based on the provisions of Directives 2004/23/EC, 2006/17/EC and 2006/86/EC is proposed in Annex 10. This format could facilitate establishment of the public CA registry for TEs required by Directive 2004/23/EC (Article 10) and of a network linking the national tissue establishment registers, as required by Article 10(3). The proposed format includes only the minimum information that should always be included in the certificate and in the CA's register of authorised TEs. Further information could be added to meet the CA's own requirements. It would not be published in the public register, but would be part of the national register kept by the CA.

This format can be used irrespective of whether or not the CA bases the initial accreditation, designation, authorisation or licensing on on-site inspections.

Any CA should, at the request of another CA, provide a copy of a TE's authorisation certificate.

Figure 1: Inspection process



7.0 Inspectorate quality management system

All competent authorities should have a quality management system in place comprising adequate SOPs and an appropriate internal audit system. They should regularly conduct an evaluation of their inspection systems in the light of their specified procedures. Information that could be useful for developing the quality management system is listed below.

7.1 System performance

Each CA should establish its own indicative list. As a minimum, the following performance indicators should be evaluated regularly:

- Number of inspection visits conducted per year;
- Number of centres accredited/designated/authorised/licensed per year;
- Average time from inspection to final report;
- Number of processes assessed per year;
- Number of processes authorised per year;
- Average time from application for authorisation of the process to final report;
- Comparison of outcomes of subsequent inspections.

7.2 Inspector performance

Inspectors and experts, where used, should be subject to an annual review of their performance which should include identification of training needs. Some of the key performance indicators that should be regularly reviewed include:

- Number of inspections performed by each inspector per year;
- Number of centres accredited/designated/authorised/licensed by each inspector per year (if applicable);
- Average time taken by each inspector from inspection to final report;
- Number of processes assessed (where applicable) by each inspector per year;
- Number of processes authorised (where applicable) by each inspector per year.

7.3 Inspector skills

The system should include periodic evaluation, e.g. by senior or specialist inspectors observing inspection visits, to assess the inspector's skills in the following areas:

- The extent and depth of the inspection;
- The ability to recognise deficiencies;
- The assessment of the seriousness of deficiencies;
- The action recommended;
- The effectiveness with which the action decided is carried out.

Note: These indicators should be adapted to the type, size and complexity of the TEs inspected.

Annex 1: Procurement and Donor Testing

Procurement

Inspectors must check whether the procurement organisation complies with the requirements laid down by Directive 2006/17/EC and with the implementing measures in the MS.

Donation and procurement practices may be verified:

- either indirectly by auditing these services at the TE;
- or directly by a specific site inspection at the organisation where these activities take place.

The following methods are recommended for verifying compliance with these requirements:

Review of documents

- Organisation chart: job descriptions, qualifications and competence of the nominated medical practitioner and qualifications and training of staff;
- Authorisation and accreditation of the conditions for procurement (if the CA is not in charge of authorisation);
- Donor records: SOPs and records;
- Procurement process: SOPs and records;
- SOPs on verification of donor's identity;
- SOPs on assessment of selection criteria for deceased (beating and non heart beating) and living donors;
- SOPs for obtaining blood samples for serological and/or NAT testing of donors, identification and handling of the samples and validation and assessment of the laboratory tests;
- SOPs for packaging, labelling and transport, if applicable;
- Traceability system (e.g. coding of the procured tissues or cells);
- Documentation accompanying the tissues or cells to the TE;
- SOPs for management of SAE and SAR.

Interviews with staff

- Interviews with selected staff to assess their knowledge and understanding of the procedures and the adequacy of the training provided.

Observations and examinations

- Inspectors should check that donor selection and evaluation were performed by trained personnel in accordance with SOPs and described in detail in records. Donor selection and screening records should be reviewed by inspectors for compliance with the requirements regarding donor identity, consent details,

information provided, medical history, assessment of selection criteria and behavioural risks, detailed physical examination and assessment of the results of laboratory testing.

- Inspectors should check for evidence that, in the case of living donors, face-to-face interviews are conducted in accordance with Annex I to Directive 2006/17/EC.
- Inspectors should check that, in the case of deceased donors, the cause, time and circumstances of death are recorded. They should also confirm that national and local requirements for confirmation of death were complied with before tissue procurement began.
- Inspectors should select a number of donor records at random to confirm that the TE complies with the donor exclusion criteria laid down in Annex I to Directive 2006/17/EC. This review should confirm that the donor's behavioural history (of relevance to increased risk of disease transmission) has been reviewed. Particular attention should be paid to tumours, infections and risk factors for transmissible diseases.
- Inspectors should verify that all the mandatory biological tests have been carried out in accordance with the applicable legislation. In the case of deceased donors, blood samples should have been obtained prior to death or, if not possible, within 24 hours of death. In the case of living donors, blood samples should be obtained at the time of donation or, if not possible, within seven days after donation.
- Inspectors should check that blood samples used for testing are not diluted by prior transfusions or infusions which would render the test result invalid.
- Procurement conditions: Inspectors should check that tissue and cell procurement are performed in appropriate rooms by trained personnel and that qualified equipment and methods described in detail in SOPs are used. The facilities should have a dedicated area for deceased donors. Inspectors should check that appropriate procedures and aseptic techniques for decontamination and cleaning are followed in order to avoid cross-contamination or an increased level of contamination. Sterile single-use instruments should be used whenever possible. Equipment and instruments used should be qualified, and sterilised between procurements, in accordance with a validated method.
- In the case of living donors, procurement must occur in an environment that ensures their health, safety and privacy.
- Transport: Inspectors should examine the appropriateness of the area where the tissues or cells are temporarily stored before shipment and transport to TE (including temperature control). They should examine a few packaging containers and their labels and evaluate their suitability. They should check for evidence of the sterility of the primary packaging at the time of use and whether the integrity and required storage and/or transport conditions for the tissues or cells are maintained.
- If the inspection of the tissue establishment, where the tissues or cells are processed and distributed, occurred before the inspection of the procurement establishment/organisation, inspectors may cross-check at random clinical and biological data or any other relevant data on the donors against the donor records in the TE.

Donor records

For each donor, a record must be kept containing:

(a) The donor's first name, family name and date of birth; if both a mother and child are involved in the donation (e.g. umbilical cord blood or placenta), both the name and date of birth of the mother and the name, if known, and date of birth of the child;

(b) Age, sex, medical and behavioural history (the information collected must be sufficient to allow application of the exclusion criteria, where required);

(c) Outcome of body examination, where applicable;

(d) Haemodilution formula, where applicable;

(e) The consent/authorisation form, where applicable;

(f) Clinical data and the results of laboratory and other tests carried out;

(g) 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 on the autopsy must be recorded);

(h) For haematopoietic progenitor cell donors, the donor's suitability for the chosen recipient must be documented. For unrelated donations, when the organisation responsible for procurement has limited access to recipient data, the transplanting organisation must be provided with donor data relevant for confirming suitability;

(i) For non-partner gamete donation, genetic screening for autosomal recessive genes known to be prevalent, according to international scientific evidence, in the donor's ethnic background. An assessment of the risk of transmission of inherited conditions known to be present in the family must be also carried out. The donor must give consent to all these checks;

(j) In the case of living donors, an assessment of any potential health risks to themselves (e.g. fitness of a bone marrow donor to receive a general anaesthetic or superovulation, sedation or the risks associated with the egg collection procedure in an egg donor).

Records must comply with the data protection legislation and must be legible and permanent. Data protection and confidentiality measures must be in place, in accordance with Article 14 of Directive 2004/23/EC.

Procurement report

For each tissue or cell procurement, a procurement report must be passed on to the TE. This report must contain at least the following details:

(a) The name and address of the TE to receive the cells or tissues;

(b) Donor identification data (including how and by whom the donor was identified), in accordance with the applicable data protection legislation;

(c) A description and identification of the procured tissues and cells (including samples for testing, where appropriate);

(d) The identity of the person responsible for the procurement session, including his or her signature;

(e) The date, time (where relevant, start and end) and place of procurement and the procedure (SOP) used, including any incidents that occurred; where relevant, environmental conditions at the procurement facility (description of the physical area where procurement took place);

(f) The date, time and person who obtained samples for biological tests;

(g) In the case of deceased donors, the conditions under which the cadaver was kept: refrigerated (or not) and time of start and end of refrigeration;

(h) ID/batch numbers of reagents and transport solutions used (if applicable);

(i) In the case of deceased donors, the report must also indicate the date and time of death.

Where sperm is procured at home, the procurement report must state this and need contain only:

(a) The name and address of the TE to receive the cells/tissues;

(b) The donor identification (if applicable);

(c) A signature by the donor confirming that the sperm is his.

Donor testing

Compliance with the testing requirements laid down in Directive 2006/17/EC should be verified by means of:

- Either inspections of donor testing laboratories:

When the testing is performed outside the TE or procurement organisation and the CA is not competent for inspecting such a laboratory, inspectors should, during a general system-oriented inspection, request evidence that the outside laboratory has been accredited, designated, authorised or licensed by the appropriate CA or authorities to perform those tests. Inspectors inspecting TEs should:

  - Request a copy of the authorisation certificate or check with the other CA that the appropriate authorisation for tissue and cell donor screening has been given;
  - Request the TEs to confirm how they check compliance by the testing laboratories with the requirements;

- Request the TEs to confirm how they check continued compliance with the requirements. The means by which this confirmation was established should be reviewed during the TE inspection.

- Or as part of the general system-oriented inspection of the TE/procurement organisation:

When the laboratory is part of a TE, the inspector should:

- Check if the testing described in procedures complies with the requirements of the national regulations transposing Directive 2006/17/EC;
- Examine the testing carried out in practice and look at a representative number of files to verify that it complies with the national regulations transposing Directive 2006/17/EC;
- Review SOPs.

Annex 2: Reception, Processing, Storage and Distribution

Reception: Verification of control of incoming tissues and cells

Inspectors must check whether the TE (including ITEs) verifies that incoming tissues and cells comply with the requirements laid down by Directive 2006/17/EC and with the implementing measures in the MS.

The system should be reviewed in full, paying particular attention to the aspects listed below.

The following methods are recommended for verifying compliance with these requirements:

Review of documents

- Donor/family consent or authorisation;
- Documentation on the donor's medical and behavioural history;
- Donor testing;
- Donor identification and physical examination;
- Donor history review and acceptance/rejection;
- Procurement documentation;
- Labelling, packaging and transport of procured tissues or cells;
- Tissue and cell procurement procedure;
- The referral process for potential donors;
- The system for ensuring traceability while protecting confidentiality.

Interviews with staff

The person responsible for donor selection should be interviewed. If this person is not the nominated medical registered practitioner, then ideally the nominated medical registered practitioner should also be present. If a separate organisation plays a significant role (e.g. a transplant coordination office), it should also be invited to attend.

Observations and examinations

In some cases, it can be useful for inspectors to cross-check the procurement information collected during the inspection at a TE or ITE by means of a site inspection of a procurement establishment or third country supplier.

Processing

Inspectors must check whether the TE complies with the requirements laid down by Annex II to Directive 2006/86/EC and with the implementing measures in the MS.

Inspectors must check whether the information provided in the TED and PPD is accurate and if the processes applied are compatible with the equipment and facilities used by the TE.

The following methods are recommended for verifying compliance with these requirements:

Review of documents

- SOPs;
- Processing records;
- Results of the classification of processing areas (including a review of the documented evidence that supports the reported classification);
- Procedures and data to ensure and demonstrate continued compliance with the classification (including particle counting, environmental microbial sampling and procedures for entering the area, including gowning procedures);
- Procedures to avoid cross-contamination;
- Procedures to ensure appropriate restricted access and protection of confidential data;
- Procedures for SAE/SAR reporting.

Interviews with staff

Interviews with selected staff to assess their knowledge and understanding of the procedures.

Observations and examinations

- Inspection of the processing (controlled) area. Particular attention should be paid to:
    - Flow of staff, incoming tissues and cells, final products and waste through the area;
    - Arrangement, size and operation of changing rooms between classified areas;
    - Procedures for changing, gowning, hand-washing, etc.;
    - Appropriateness of surfaces, equipment, etc.;
- Observation of processing being performed, if possible;
- Review of any reports of serious adverse events or serious adverse reactions linked to processing and the associated corrective action.

Storage and distribution

Inspectors must check whether the TE complies with the requirements laid down by Annex II to Directive 2006/86/EC and with the implementing measures in the MS.

Inspectors should check whether the information provided in the TED is accurate.

The following methods are recommended for verifying compliance with these requirements:

Review of documents

- SOPs for storage;
- SOPs for distribution;
- SOPs for traceability;
- SOPs for recall;
- SOPs for labelling (immediate and container);
- Agreements with third parties who may distribute tissues or cells on behalf of the TE.

Interviews with staff

Interviews with selected staff responsible for storage and distribution.

Observations and examinations

- Inspection of the storage area. Particular attention should be paid to:
    - Control of relevant physical conditions (e.g. temperature and humidity);
    - Clear separation between tissues or cells in quarantine and 'released for distribution';
    - The system for authorising and executing the transfer of tissues or cells from quarantine to 'released for distribution';
    - The system used for tissue and cell identification and traceability at each step of the process (e.g. coding, labelling and IT system);
    - Biohazard waste (restricted area, security, handling, packaging and labelling, etc.);
- Examination of labels, including the label on the final tissue or cell package;
- Examination of storage temperature records;
- Examination of traceability, by selecting finished tissues and cells available for distribution and requesting information on:
    - The donor's history;
    - The date and time when they were processed;
    - The identity of the person who carried out the processing;
    - Which batch/lot numbers of reagents or additives were used, with expiry dates;
    - Which equipment was used and, if applicable, its maintenance and qualification status;
    - Specifications for each step of the processes;
    - Which environmental conditions the tissues or cells were exposed to (including storage locations);
    - What type of microbiological testing was performed and the results (including the results of microbiological control of cell-based products, as prescribed by the European Pharmacopeia, or alternative controls acceptable to the CA);
    - Who released the tissues or cells and on what basis.
- Review of documentation on particular requests for tissues and cells and of tissues or cells distributed ;
- Examination of package label information issued with tissues or cells;

- Review of any reports of serious adverse events or serious adverse reactions and the associated corrective action;
- Review of at least one maintenance and calibration record for a critical piece of storage equipment selected by the inspection team;
- Review of one example of a document confirming authorisation to transfer the tissues or cells from quarantine to distribution.
- Inspectors should review representative examples of donor documentation on tissues or cells available for distribution or distributed in the last year and on tissues and cells in quarantine or that have been imported/exported. Whenever possible, the files should be selected by the inspection team and should include files for tissues or cells observed in the TE or 3CS inventory. On occasions it might be necessary to examine files for tissues or cells that have passed their expiry date.

Annex 3: Assessment of Preparation Processes

Inspectors must check whether the TE complies with the requirements laid down by Annex II to Directive 2006/86/EC and with the implementing measures in the MS.

Processes which are simple, well established and widely applied can be adequately assessed during a general system-oriented inspection (see Annex 2).

It is recommended that preparation processes should be assessed separately during a thematic inspection of the preparation process if the process is complex, innovative or unique to a particular TE.

Before the inspection

- The TE should submit a revised preparation process dossier - PPD (see Annex 9) - (or a new addendum to the PPD) for authorisation of the new process.
- The PPD should be assessed on the basis of a thorough documentation review before or after an inspection. The findings of such reviews can be confirmed during a subsequent on-site inspection.

During the inspection

The inspection should be performed by a minimum of one assessor or inspector and, ideally, unless the assessor or inspector is a technical expert in the process steps concerned, one or more experts in a field relevant to the process under consideration. Experts should consult other specialists where necessary (see point 6.1).

The following aspects should be verified during the inspection:

1. Evaluation of Validation Reports

Tissue establishments are required to demonstrate that critical tissue and cell processing procedures have been validated and do not render the tissues or cells clinically ineffective or harmful to the recipient/patient. There is no requirement for centralised approval of a particular processing procedure or for studies demonstrating clinical effectiveness.

Directive 2006/86/EC allows validation studies to be based on any of the following:

Studies performed by the establishment itself

The reports should include at least:

- A validation plan which specifies the critical parameters to be assessed and the acceptable result thresholds for these parameters;
- A documented methodology;
- All results obtained, in a clear form with relevant interpretation;
- A signed declaration of acceptance or rejection of validation by the quality manager or the RP.

Data from published studies

The publications should be made available for review. In this case, TEs should demonstrate that they can effectively reproduce the published process with the same results in their facility (operational validation). Copies of the relevant standard operating procedures and the results of the operational validation should be provided to demonstrate that the process is equivalent to that applied in the published study. Where specific steps have been changed or adapted, separate validation should confirm that these changes have not invalidated the method. A signed declaration of acceptance or rejection of validation by the quality manager or the RP should be included.

In the case of well established processing procedures, retrospective evaluation of the clinical results for tissues and cells supplied by the establishment can be used.

Evidence should be provided of the number of tissue or cell grafts implanted following processing by the method under consideration and the period during which these implantations occurred. Where a vigilance system was already in place at the time, it should be demonstrated that clinical users were informed of the procedure for reporting adverse reactions. A signed declaration of acceptance or rejection of validation by the RP should be included.

2. Evaluation of Risk Assessment Reports

Where new preparation processes are introduced, risk assessments will commonly have been performed as part of the changeover process. See Annex 4 for guidance on the review of risk assessments during inspection or during the assessment of preparation processes.

Advanced Therapies Medicinal Products

Substantially manipulated tissues and cells not intended to be used for the same essential function or functions in the recipient as in the donor are considered to be 'engineered' and are regulated by the Advanced Therapy Medicinal Products (ATMP) Regulation[7].

Processes included on the list in Annex I to the ATMP Regulation are considered not to be 'substantially manipulated' and fall under the Tissues and Cells Directives, i.e. cutting; grinding; shaping; centrifugation; soaking in antibiotic or antimicrobial solutions; sterilisation; irradiation; cell separation, concentration or purification; filtering; lyophilisation; freezing; cryopreservation; and vitrification.

This list is not exhaustive; processes used in assisted reproduction technology (ART) are not considered 'substantially manipulated'.

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[7] Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004 (OJ L 324, 10.12.2007, p. 121).

The borderlines between ATMP and tissues and cells might not be clear in some cases. In this regard, Article 17 of Regulation 1394/2007 allows developers of a product based on genes, cells or tissues to request a scientific recommendation from the Agency[8] with a view to determining whether the product concerned falls, on scientific grounds, within the definition of an advanced therapy medicinal product.

(For further information and assessment, see: AdvancedTherapies@ema.europa.eu).

When an opinion has been issued on this respect, either by the Committee on Advanced Therapies (CAT) or by the competent authorities in the Member State, it should be kept together with the tissue establishment dossier or the preparation process dossier.

[8] European Medicines Agency.

Annex 4: Evaluation of Risk Assessment Reports

Directives 2004/23/EC, 2006/17/EC and 2006/86/EC lay down several legal requirements for performing a risk assessment when managing tissues or cells for human use. Transplantation to human patients carries a risk of disease transmission which can be significantly reduced by adopting practical and scientific measures at the TE. This can be achieved by applying new techniques or revised procedures which are updated in line with the best scientific advice.

Inspection programmes should verify that each TE fulfils its duty to perform risk assessments to determine the fate of stored tissues and cells when new donor selection or testing criteria or any significantly modified processing step which enhances quality or safety are introduced (Annex II, point C. 5 in Directive 2006/86/EC). This approach takes on more significance when the inspection process identifies tissues or cells which were donated, tested and stored earlier, in accordance with pre-existing national regulations and/or professional practices which might not fully comply with the existing regulations. For example, the biological testing requirements, the donor screening practices or the traceability systems are likely to be more stringent today than in the past. Exceptionally, in the case of limited availability and expected clinical benefit, the stored tissues and cells may well be considered for use in circumstances where interested parties are fully informed of their status and the alternative therapeutic options.

Annex I to Commission Directive 2006/17/EC requires a documented risk assessment, approved by the responsible person, as defined in Article 17 of Directive 2004/23/EC, to justify acceptance of a donation even though one of the listed exclusion criteria applies. It also requires performance of a risk assessment where donor travel or exposure history imply a risk of infections for which testing is not normally performed.

Annex II to the same Directive requires a documented risk assessment to justify clinical use of tissues or cells from donors who either test anti-HBc positive and HBsAg negative or who are reactive on a Treponema-specific test.

Inspectors should verify that a risk assessment applying a methodical approach to scientific evaluation of the related aspects was concluded at the TE concerned in order to allow an appropriate decision to be reached. All risk assessment plans should include documentation on:

- The scope/circumstances for conducting the assessment;
- The individuals assigned to the work programme;
- Identification of the hazards associated with the scope/circumstances;
- An estimate of their severity (impact) and probability of occurrence (likelihood);
- The risk analysis, evaluation and control measures for these hazards;
- The scientific grounds for acceptance/rejection of the decision;
- A rationale for the acceptability of the residual risk;
- An acceptance statement by the RP/parties on the residual risk.

A similar approach can equally be applied for other risk assessments to evaluate and support procurement/third-party activities and practices/systems adopted for minimising the risk of infection to patients. For example, it can be relevant to:

- Management of donor selection practices/protocols;
- Receipt of tissues or cells at the TE;
- Intermediate storage of donations awaiting biological test results;
- Policy on storage systems for tissues and cells suspected or known to be positive;
- Formal release of processed tissues and cells for storage or distribution;
- The rationale for patient use in exceptional cases of direct distribution;
- Implementation of new or significantly modified processes.

Management plans should identify and describe the principal activities of the TE (e.g. by means of a flowchart) and the circumstances to which the different phases of the plan apply. All components of the risk management process should be linked to the authorised/licensed activities of the TE. Its level of detail should be related to the known and perceived risks associated with the different types of tissues or cells. It should be integrated into the quality system.

Informative guidance on application of and tools for risk assessment are provided in the International Standard on Application of Risk Management to Medical Devices (EN ISO 14971) and in Annex 20, Quality Risk Management, of the EU Guidelines to Good Manufacturing Practice of Medicinal Products for Human and Veterinary Use (GMP Annex 20)[9].

[9] http://ec.europa.eu/health/files/eudralex/vol-4/pdfs-en/2008_02_12_gmp_annex20_en.pdf

Annex 5: Import/Export — Verification of Technical Requirements

The purpose of this Annex is to provide guidance to competent authorities of the EU Member States on carrying out inspections of importing tissue establishments (ITEs) and / or their third country suppliers (3CSs) as well as on the export and direct distribution of tissues and cells. This guidance is supplementary to the guidance found elsewhere in this manual which is also relevant for inspections of ITEs and 3CSs.

Article 4 of Directive (EU) 2015/566 states that:

1. *Member States shall ensure that the competent authority or authorities organise inspections and other control measures of importing tissue establishments and, where appropriate, their third country suppliers and that importing tissue establishments carry out appropriate controls in order to ensure the equivalency of the quality and safety standards of the tissues and cells to be imported with the standards laid down in Directive 2004/23/EC. The interval between inspections of any given importing tissue establishment shall not exceed two years.*

2. *Such inspections shall be carried out by officials representing the competent authority or authorities who shall:*

(a) *be empowered to inspect importing tissue establishments and, where appropriate, the activities of any third country suppliers;*

(b) *evaluate and verify the procedures and activities carried out in importing tissue establishments and the facilities of third country suppliers that are relevant to ensuring the equivalency of the quality and safety standards of the tissues and cells to be imported with the standards laid down in Directive 2004/23/EC;*

(c) *examine any documents or other records that are relevant for this evaluation and verification.*

Further details of the legislative requirements can be found in Article 9 of Directive 2004/23/EC and Commission Directive (EU) 2015/566.

Two types of inspections are thus possible: Inspections of ITEs and inspections of 3CSs and these will be considered in turn below.

INSPECTIONS OF IMPORTING TISSUE ESTABLISHMENTS

Only ITEs authorised for this purpose can import tissues and / or cells from third countries[10]. Inspections of ITEs may be carried out as part of a general inspection of the establishment or a specific inspection looking at its import activities.

Inspection of this activity should address:

[10] 'Third countries' are those outside of the EU and EEA countries

- The types of tissues and cells intended for import and the reason for choosing to import;
- The procedures carried out by the ITE to ensure the equivalency of the quality and safety standards of the tissues and cells to be imported with the EU quality and safety standards;
- The 3CS and the activities they perform;
- The authorisation of the 3CS and scope of authorisation; i.e. whether the 3CS are authorised to perform the relevant activities for the specific tissues and cells to be imported;
- The nature of the arrangement between the ITE and 3CS, i.e. whether it is a routine supply arrangement or a 'one-off' arrangement;
- The written agreement between the ITE and 3CS where applicable (certain one-off arrangements may be exempt from the requirement to have a written agreement between the ITE and 3CS);
- Details of the flow of imported tissues and cells from their procurement to their reception at the ITE;
- The reception of imported T&C at the ITE and activities carried out by the ITE subsequent to the import.

1.1 Inspection Procedures

Inspections of ITEs should, as a general rule, be conducted following the guidance on inspection procedures in section 6.0 of this manual. The guidance in Annex 2 of this manual relating to tissue and cell reception is also of particular relevance for inspections of ITEs. Furthermore, the guidance on steps to take before and during inspections in third countries in section 2.1 of this Annex may also be relevant for inspections of ITEs, in particular where a joint inspection or the participation of inspectors from another EU Member State is envisaged.

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

There are two types of importation that may be undertaken;

- Routine importation;
- "One-off" importation.

Routine Importation

In the case of routine importation, the ITE should assess the quality and safety systems in place at the 3CS in order to verify that the standards of quality and safety of the tissues and cells they import are equivalent to the standards of quality and safety laid down in the EU Tissue and Cell Directives.

Inspections of ITEs should thus include an examination of the documentation relating to the assessment made by the ITE of the quality and safety systems at its 3CS. This should cover both 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 biovigilance, licences and accreditation, etc;
- Documentation relating to the review of the safety and quality of individual dispatches of tissues or cells, e.g. Confirmation of donor consent, confirmation of donor sample testing performed and their results, donor suitability, description of the tissues or cells, transport arrangements, etc.

The full list of documentation required for importation is listed in Annex I and Annex III to Directive (EU) 2015/566.

The inspector should examine the written agreement in place between the ITE 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 of the required minimum contents as laid down in Annex IV to Directive (EU) 2015/566.

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

- Determine how the ITE ensures that the tissues and cells it imports into the Union meet quality and safety standards equivalent to those in place in the Union;
- 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, whether 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;
    - Arrangements for the transportation of the tissues and cells;
- Determine if the ITE audits its 3CS and, if so, how this is done;
- 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.

'One-off' Importation

One-off imports are defined in Article 2(c) of Directive (EU) 2015/566. Articles 5 and 7 of this Directive give MS the discretion to choose to not apply the documentation requirements of Annex I part F and Annex III and the requirements for written agreements between the ITE and 3CS. In such situations MS must have suitable national measures in place to regulate the import and ensure traceability from donor to recipient and vice versa and that the tissues and cells are applied to the intended recipient.

In cases of one-off importation, the inspection should include an examination of the ITE's documented evaluation of the safety and quality of the tissues or cells imported. Of particular importance in the case of one-off importation is:

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

After the Inspection

Following an inspection of an ITE and in addition to the guidance in section 6.3.1 of this manual, the inspector should produce a written inspection report in his/her national language and, in addition, where dissemination to authorities from other countries or the Commission is foreseen, the main relevant findings should be summarised in English.

In certain circumstances, the inspector may consider it necessary to make further enquiries, re-inspect the ITE and / or inspect its 3CS, or request additional information on corrective actions before taking a final decision (on whether or not the ITE can continue to import from the 3CS in question).

Dissemination of Information

Where a MS or the Commission requests information on an inspection this should be provided following the inspection as per Article 4(3) of Directive 2015/566/EU which states:

Member States shall, upon a duly justified request from another Member State or the Commission, provide information on the results of inspections and other control measures relating to importing tissue establishments and third country suppliers.

Where the results of an inspection uncover serious quality and the safety defects relating to imported tissues and cells, the CA should consider the need for a Rapid Alert to inform other MS CAs using the Rapid Alert for Tissues and Cells (RATC) Platform. Where a Rapid Alert is launched the ITE should be informed of this action. Any change in the authorisation status of an ITE resulting from an inspection should be updated in the EU Tissue Establishment Compendium as well as national tissue establishment registers.

For inspections conducted at the request of a CA or agency from another sector or country, the report should be made available to the requesting organisation.

INSPECTIONS OF THIRD COUNTRY SUPPLIERS

Directives 2004/23/EC and (EU) 2015/566 place responsibility on ITEs to verify that the organisations from which they import tissues or cells work to quality and safety standards equivalent to those specified in the EU tissues and cells Directives. However, in certain cases CAs may consider it necessary to go to a supplier of tissues or cells in a

third country and conduct an inspection. The reasons for conducting such inspections might include:

- Multiple ITEs are importing from a particular 3CS;
- A high volume of tissues or cells are being imported from a particular 3CS;
- There is evidence of (continued) poor performance, an issue of non-compliance or a suspicion of illegal or fraudulent activity[11] by a 3CS;
- A SAR/SAE has been associated with the tissues or cells concerned;
- An inspection of the ITE uncovered concerns related to the 3CS;
- An inspection request has been made by a CA or agency from another sector or country;
- A substantial change in the ITE's import activities[12].

2.1 Inspection Procedures

As a general rule, inspections in third countries should be conducted following the general guidance on inspection procedures in section 6.0 of this manual. In addition the guidance below is particularly relevant for inspections of 3CS.

Before the Inspection

Where the competent authority or authorities choose to inspect the activities of 3CS, the preparation of the inspection should comply with the following requirements:

- Inform the relevant authority or authorities in the third country, obtain any necessary permission and fulfil any legal requirements prior to departure;
- Additionally, an inspector may choose to inform the ITE(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 competent authority to participate in the inspection. Where the 3CS to be inspected exports tissues and / or cells to ITEs located in more than one Member State 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. Article 4 of the Directive lays down that:

(4) Member States into which tissues and cells are imported shall, upon a duly justified request from another Member State into which imported tissues and cells are subsequently distributed, consider carrying out inspections or other control measures on importing tissue establishments and the activities of any third country suppliers. The Member State in which the importing tissue establishment is located shall decide on the

[11] A guide on investigating illegal or fraudulent activity has been developed as part of the SoHO Vigilance and Surveillance Project and is available for inspectors and competent authorities on request from the project leaders: http://www.sohovs.org/soho/mod/resource/view.php?id=40

[12] Article 3(3) of Directive (EU) 2015/566 states that, in particular, any changes to the type of tissues and cells imported, the activities undertaken in third countries which may have an influence of the quality and safety of imported tissues and cells or the third country suppliers used shall be considered as substantial changes.

appropriate measures to take following consultation with the Member State which made such a request.

(5) Where an on-site inspection takes place following such a request, the competent authority or authorities of the Member State in which the importing tissue establishment is located shall agree with the competent authority or authorities of the Member State which made such a request on whether and how the Member State which made such a request shall participate in the inspection. The final decision on any such participation shall rest with the Member State in which the importing tissue establishment is located.

In such a situation, agreement should be reached on how the requesting MS' inspector(s) will participate in the inspection before the inspection takes place.

Before the inspection at the 3CS, the inspector should enquire about the existence of the following information:

- If there is any additional information available from a trusted source (e.g. an inspection had recently been performed by another MS which deemed the site (non-)compliant);
- If the site of the 3CS was recently inspected by a third country authority with a favourable or unfavourable outcome;
- Determine if the 3CS has been authorised, licensed or accredited by its national CA or if it is exempt and for which activities and for which products;
- Determine if the 3CS is, in addition, a member of, or applying for membership of, any accrediting organisation and whether it is accredited or if it has been accredited in the past;
- Clarify if 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 ITE / trusted source / third country authority, including:

- Verification of the (export) authorisation and its scope;
- Verification that the written agreement accurately reflects the one provided by the ITE;
- Verification that the procedures relating to prescribed activities, performed by the 3CS or subcontractor, are in accordance with the detailed information provided by the ITE;

In addition the inspector should:

- Perform a detailed tour of the facilities to assess the specifications of the areas where the tissues or cells are procured, processed and temporarily stored prior to distribution and transport to the ITE;
- Review the information provided in the documentation which accompanies the exported tissues and cells: Such as who should be contacted in case of SAE/R? and the accuracy of the information provided to the end user.(The

documentation which accompanies the products such as: Courier forms, which should be in the national language of the ITE);

- Determine the number of donors per year from whom the 3CS procures and / or processes tissues and / or cells, inspectors may cross-check at random clinical and biological data or any other relevant data on the donors against the donor records in the ITE;
- Select a number of donor records at random to confirm that the 3CS or its sub-contractor complies with the donor exclusion criteria laid down in Annex I to Directive 2006/17/EC. This review should confirm that the donor's behavioural history (of relevance to increased risk of disease transmission) has been reviewed. Particular attention should be paid to tumours, infections and risk factors for transmissible diseases;
- Review donor screening policy, information on the testing centre(s) and the tests performed and verify whether the tests meet EU testing standards.

After the Inspection

Following completion of the inspection and in addition to the guidance in section 6.3.1 of this manual and section 1.1 of this Annex the inspector should:

- Produce a written inspection report containing general information on the 3CS and the CA of the third country, a description of the inspection and the observations and conclusions arising from it. The conclusions of the report should clearly identify any deficiencies, classifying them as critical, major or other;
- Make the report available to the ITE and 3CS based on the relevant national procedures for doing so;
- Where the inspection has uncovered deficiencies, set a date by which the ITE (where necessary in conjunction with its 3CS) shall submit proposals and a schedule for rectifying the deficiencies outlined in the report (corrective action plan). The inspector should evaluate the proposed action plan and, on that basis, make a recommendation to the relevant authority in the third country in line with the specific mandate of the inspection, clearly stating whether or not the 3CS complies with the requirements of this Directive;
- Inform the ITE and 3CS of the final decision in writing.

Dissemination of Information

The guidance on dissemination of information in part 1.1 of this Annex is also applicable to the dissemination of information on inspections of 3CS.

TISSUE AND CELL EXPORTS BY TISSUE ESTABLISHMENTS

Only TEs authorised for this purpose may export to third countries. Inspections of this activity should address the following points:

- Verification that only tissues or cells meeting the requirements for human application in the EU are being exported for human application outside the EU, unless special circumstances apply, such as export for use in an approved clinical

trial with specified safety and quality requirements that differ from those laid down in the Tissues and Cells Directives.

- A representative number of donor and procurement records should be reviewed to ensure that equivalent safety and quality standards are applied to the tissues or cells concerned.
- Where tissues or cells not meeting the normal requirements are exported on the basis of a risk assessment, this should be reviewed to ensure that it was conducted adequately and that all relevant parties involved were aware of any deficiencies and agreed to the risk/benefit analysis. For further information on management of risk assessment, see Annex 4.

AUTHORISATION OF IMPORT/EXPORT INVOLVING DIRECT DISTRIBUTION

Directive 2004/23/EC provides for the distribution of tissues or cells in case of emergency directly from a collection centre to a clinical centre. As normally no TE is involved, in the case of direct distribution from a third country, the CA is responsible for authorising the import/export and may apply more stringent criteria than those specified in the Directives.

Direct distribution applies primarily to haematopoietic stem cells and, in some cases, to tissues and cells for assisted conception.

In general, import/export and delivery to the clinical centre should be permitted in quarantine and authorisation should be provided rapidly, taking into consideration the short life and unique nature of the tissues or cells and the condition of the intended recipient. This should not prevent the competent authorities from taking the appropriate measures to ensure that direct imports and exports of tissues and cells meet quality and safety standards equivalent to those laid down in the Directives.

The request for authorisation will be made by the clinical centre that will apply the material and, in some cases, by a national or regional transplant registry. Inspectors must check that the review conducted by the physician or by the national or regional transplant registry includes:

- Reasons for import/export**;**
- Documentation from the registry or the clinical centre on equivalence of safety and quality (including any certificates and/or authorisations granted);

Where information is missing or full compliance with the EU Directives cannot be demonstrated but the clinical centre wishes to proceed, the documented risk assessment performed by the clinical centre (or registry) should be reviewed.

Annex 6: Proposed Common Format for a Tissue Establishment Dossier

Tissue Establishment Dossier

(TED)

Please complete one dossier for each site if the TE has more than one site

Section A — General Information

Full name of TE:	
Name of responsible person, as defined in Directive 2004/23/EC: **(Please attach a curriculum vitae.)**	
Name of quality system manager (where applicable): **(Please attach a curriculum vitae.)**	
Postal address of TE:	
Telephone number:	**Fax number:**
E-mail address:	

Summary of activities

Type of tissues or cells	Prescribed activity (PA) (Please insert PA code(s) from key below.)	Preparation processes (PP) applied (Please insert PP code(s) from key below.)
Skeletal □		
Skin □		
Vascular □		
Ophthalmic □		
Amniotic membrane □		
Ovarian □		
Testicular □		
Other tissue □ …….....		
Bone marrow □		
PBSC □		
Cord blood □		
Oocytes □		

Spermatozoa □

Other cells □

……...

Embryos □

Zygotes □

Other □

…….....……

PRESCRIBED ACTIVITY CODES			
Donation: PA1	**Procurement: PA2**	**Testing: PA3**	**Processing: PA4**
Storage: PA5	**Distribution: PA6**	**Import: PA7**	**Export: PA8**

PREPARATION PROCESS CODES			
Cutting/grinding/shaping	**PP1**	Demineralisation	**PP13**
Centrifugation	**PP2**	Storage in organ culture medium	**PP14**
Soaking in antibiotic or antimicrobial solutions	**PP3**	Storage at 4°C	**PP15**
Sterilisation (not by irradiation)	**PP4**	Glycerolisation (high concentration)	**PP16**
Irradiation sterilisation	**PP5**	Thawing	**PP17**
Cell separation, concentration and purification	**PP6**	*In vitro* fertilisation (IVF)	**PP18**
Filtering	**PP7**	Intracytoplasmic sperm injection (ICSI)	**PP19**
Lyophilisation (freeze-drying)	**PP8**	Sperm preparation	**PP20**
Freezing	**PP9**	Assisted hatching	**PP21**
Cryopreservation	**PP10**	Culture to blastocyst	**PP22**
Vitrification	**PP11**	*In vitro* maturation (IVM)	**PP23**

Drying	**PP12**	Embryo/polar body biopsy	**PP24**

Reference number/code of the competent authority processing authorisation (if available):	

Section B — Activity — Details

Please attach a flowchart illustrating the full activity of the TE.

Does the TE conduct procurement?	**YES/NO**
Does the TE obtain tissues and cells from external procurement organisations?	**YES/NO** If yes, please indicate which procurement organisations:
Does the TE conduct donor testing?	**YES/NO** If no, please indicate which organisation(s) conduct(s) testing of the tissue/cell donors:

Types of tissues/cells/substances of human origin received by the TE (from own procurement or procurement by others):	Please list here or attach a separate list:
Number of donors from whom tissues/cells were received at the TE in the previous year (should be equal to the number stated in the annual report):	Living allogeneic (unrelated, non-partner): Living allogeneic (related or partner): Living autologous: Deceased:
Types of tissues/cells processed by the TE:	Please list here or attach a separate list:

How are processing methods validated? (to demonstrate that they do not render the tissues/cells clinically ineffective or harmful for the recipient) (no need to complete this section if a preparation process dossier is used):	a) By studies conducted at your TE? ☐ b) By published studies? ☐ c) By retrospective analysis of clinical results? ☐ d) Other (please specify): ☐ …… ……
In-process and final quality control testing methods applied to the tissues or cells:	Please list here or attach a separate list:
Types of finished tissues/cells/substances of human origin distributed by the TE:	Please list here or attach a separate list:
Does the TE receive finished tissues/cells from other TEs in the same EU Member State for distribution?	**YES/NO** If yes, indicate which type of tissues/cells and provide the name(s) of the TE(s):

Does the TE receive tissues/cells from other TEs in another EU Member State for distribution?	**YES/NO** If yes, indicate which type of tissues/cells and name the country or countries of origin and the TE(s):
Does the TE import tissues/cells from outside the EU for distribution?	**YES/NO** If yes, indicate which type of tissues/cells and name the country or countries of origin and the TE(s):
Number of tissue or cell units (individual packages, bags, straws vials) distributed by the TE for human application in the previo year (should be equal to the number stated in the annual report	

Section C — Personnel

Name of TE Director (if different from the responsible person) **(please attach a brief curriculum vitae):**	
Name of Medical Director (if different from above) **(please attach a brief curriculum vitae):**	

Name of Processing Manager (where relevant)

(please attach a brief curriculum vitae):

Total number of staff:

Please provide an organisation chart indicating roles and reporting relationships

(insert in the space provided or attach separately).

Please indicate in the organisation chart how many people are working on donor selection, procurement, processing, quality control, quality assurance, administration, storage and transport.

Section D — Facilities

Please describe the processing and storage facilities. Please indicate the number of rooms, their dimensions and their environmental classification, where relevant.

(Please attach a plan of the area, giving details of the rooms (numbered), their purpose and personnel and of the tissues or cells and of the personnel, material and waste flow.)

Section E — Equipment

Please provide a list of the critical equipment used for processing and testing.

Please describe the system used to support traceability (if relevant).	

Section F — Contracts/Agreements with Other Organisations

Are any prescribed activities carried out by a third party (from procurement to	**YES/NO** If yes, indicate which activities and name the organisation that acts as the third party. Please provide copies of relevant agreements.

distribution)?

Section G — Transport and Distribution

Please describe the arrangements in place for transporting each type of tissues or cells from procurement to the TE.

Please describe the arrangements in place for transporting each type of tissues or cells from the TE to the organisation responsible for human application.

Section H — Adverse Event and Reaction Reporting

Please describe the arrangements in place for reporting and managing SAE and SAR.	

Section I — Quality Management System

Please give a brief description of the quality system applied at the TE.

Please attach a list of the SOPs in place.

Has the TE been certified by any external body or	**YES/NO**

professional society?	If yes, please give details of when and by whom and **add the certification number.**

Section J — Signature and Date

Signature of responsible person:	
Date:	

Section K — Instructions for Submission of this Form

This form should be submitted as an initial application for accreditation, designation, authorisation or licensing by the competent authority for tissues and cells. It should be re-submitted before an inspection at the request of the Inspectorate and whenever significant changes in activity, staffing or processes applied have taken place or whenever there are significant changes to any of the attached documents.

Changes considered to be significant include:

- **change of responsible person;**
- **change in activities;**
- **use of new equipment for an authorised process;**
- **signature of a new contract with new subcontractors or a new agreement with a collecting centre;**
- **transfer of one or more of the activities to new premises;**
- **cessation of activities or closure of the site;**
- **introduction of a new IT system.**

Each CA should insert relevant instructions for submission.

Annex 7: Proposed Format for an Inspection Findings Form

INSPECTION FINDINGS FORM

COMPETENT AUTHORITY:	**«Name of the competent authority»**
Name of the lead inspector: Attached unit or department:	«Name» «Attached unit or department»
Name of the inspector(s): Attached unit or department:	«Name(s)» «Attached unit or department»
Name of the technical expert (if relevant): Attached unit or department:	«Name» «Attached unit or department»

TE INSPECTED:	«Adress1» «Adress2» «Phone number» «Fax number»
Name and address of the responsible person:	«Name» «Phone number» «Fax number»
Date of the inspection:	/___/___/ /___/___/ /___/___/___/___/

Personnel	
Assessed during this inspection ☐	Not assessed during this inspection ☐

No	Observation	Comments

Facilities/Premises

Assessed during this inspection ☐	Not assessed during this inspection ☐

No	Observation	Comments

Materials and Equipment

Assessed during this inspection ☐	Not assessed during this inspection ☐

No	Observation	Comments

Quality Management System	
Assessed during this inspection ☐	Not assessed during this inspection ☐

No	Observation	Comments

Donor Selection, Donor Testing and Procurement	
Assessed during this inspection ☐	Not assessed during this inspection ☐

No	Observation	Comments

Processing, Storage and Distribution	
Assessed during this inspection ☐	Not assessed during this inspection ☐

No	Observation	Comments

Quality Control	
Assessed during this inspection ☐	Not assessed during this inspection ☐

No	Observation	Comments

Distribution Outside MS, Import and Export	
Assessed during this inspection ☐	Not assessed during this inspection ☐

No	Observation	Comments

Traceability

Assessed during this inspection ☐	Not assessed during this inspection ☐

No	Observation	Comments

Third-Party Agreements	
Assessed during this inspection ☐	Not assessed during this inspection ☐

No	Observation	Comments

Others

No	Observation	Comments

Annex 8: Proposed Common Format for a Tissue Establishment Inspection Report

TISSUE ESTABLISHMENT INSPECTION REPORT

Complete this form by replacing the italicised text

General Information	
Report reference No:	
Site(s) inspected:	*Name and full address of the site inspected.*
Summary of activities:	

Type of tissues or cells	**Prescribed activity (PA)** (Please insert PA code(s) from key below.)	**Preparation processes (PP) applied** (Please insert PP code(s) from key below.)
Skeletal ☐		
Skin ☐		
Vascular ☐		
Ophthalmic ☐		
Amniotic membrane ☐		
Ovarian ☐		
Testicular ☐		

Other tissue □ …….....		
Bone marrow □		
PBSC □		
Cord blood □		
Oocytes □		
Spermatozoa □		
Other cells □ .		
Embryos □		
Zygotes □		
Other □ ……..... ……		

PRESCRIBED ACTIVITY CODES			
Donation: PA1	**Procurement: PA2**	**Testing: PA3**	**Processing: PA4**
Storage: PA5	**Distribution: PA6**	**Import: PA7**	**Export: PA8**

PREPARATION PROCESS CODES			
Cutting/grinding/shaping	**PP1**	Demineralisation	**PP13**

Centrifugation	**PP2**	Storage in organ culture medium	**PP14**
Soaking in antibiotic or antimicrobial solutions	**PP3**	Storage at 4°C	**PP15**
Sterilisation (not by irradiation)	**PP4**	Glycerolisation (high concentration)	**PP16**
Irradiation sterilisation	**PP5**	Thawing	**PP17**
Cell separation, concentration and purification	**PP6**	*In vitro* fertilisation (IVF)	**PP18**
Filtering	**PP7**	Intracytoplasmic sperm injection (ICSI)	**PP19**
Lyophilisation (freeze-drying)	**PP8**	Sperm preparation	**PP20**
Freezing	**PP9**	Assisted hatching	**PP21**
Cryopreservation	**PP10**	Culture to blastocyst	**PP22**
Vitrification	**PP11**	*In vitro* maturation (IVM)	**PP23**
Drying	**PP12**	Embryo/polar body biopsy	**PP24**

Date of inspection: **Inspector(s):**	*Day(s), month, year* *Name(s) of the inspector(s)* *Name(s) of expert(s)/assessor(s) (if applicable)* *Name(s) of the competent authority or authorities* *e-mail address:*
Regulations on which the inspection was based:	

Brief Report on the Inspection Activities Undertaken

Introduction:	*Short description of the procurement site and/or the TE and the activities on the site (or reference to an attached TED).* *For inspections in non-EEA countries, please state whether the competent authority of the country where the inspection took place was informed of and took part in the inspection.* *Date of previous inspection.* *Name(s) of inspector(s) involved in previous inspection.* *Major changes since the previous inspection.*
Scope of inspection:	*Short description of the inspection (process-related inspection and/or general quality system inspection, with reference to specific tissues or cells where appropriate).* *The reason for the inspection should be specified (e.g. application for a new process, routine inspection, investigation of product defect, etc.).*
Inspected area(s)/activities:	*Short description of the area/activities. Please specify each area/activity inspected.*
Areas/activities not inspected:	*Where necessary, attention should be drawn to areas or activities not inspected on this occasion.*
Personnel interviewed during the inspection:	*Please specify the names and titles of key personnel met here or attach a list.*
Overview of findings from last inspection and of the corrective action taken:	*Summarise the previous findings and the corrective action taken.*

Inspector's relevant findings, including deficiencies This section can link the findings to the deficiencies and be used to explain the classification.	
Requirements for procurement and donor testing, as specified in Directive 2006/17/EC	
Selection criteria for donors of tissues and/or cells:	*Describe the findings for each type of donor (deceased, living, partner (direct use or indirect use) or non-partner).*
Laboratory tests required for donors:	
Cell and/or tissue donation and procurement procedures:	
Donor records:	
Procurement report:	
Reception at the TE:	
Requirements for accreditation, designation, authorisation or licensing of tissue establishments, as specified in Directive 2006/86/EC	
Organisation and management:	
Personnel:	
Equipment and materials:	
Facilities/premises:	
Documentation and records:	
Contracts with third parties:	
Quality review:	
Processing:	

Storage and release of tissues or cells:	
Final labelling for distribution and external labelling of the shipping container:	
Transport:	
Distribution and recall:	
Management of SAR/SAE:	
Information on the minimum donor/recipient dataset to be kept by TEs and organisations responsible for human application:	
Coding system:	
Import/Export:	
Other specific issues identified:	*E.g. relevant future changes announced by TE.*
Conclusions	
Tissue establishment dossier:	*Assessment and date of TED.*
Annexes attached:	*Please list any annexes attached.*
List of deficiencies classified into critical, major and others (see definitions at the end of this form):	*All deficiencies should be listed, giving references to the relevant national laws transposing the EU Directives.* *All deficiencies found should be listed, even if corrective action was taken immediately.* *The TE should be asked to inform the Inspectorate about the proposed schedule for corrections and on progress.* *Deficiencies should be classified on the basis of the definitions at the end of this document.*

Recommendations to the competent/enforcement authority for the site inspected:	
Summary and conclusions:	*The inspector(s) should state whether, in the course of the inspection, the TE was operating in accordance with the national laws transposing Directives 2004/23/EC, 2006/17/EC and 2006/86/EC, provided, where relevant, appropriate corrective action and should mention any other item to draw to the attention of the requesting authority. Attention should be paid to the wording used. It would be better to use conditional tenses when the TE needs to fulfil critical requirements before receiving final approval from the Inspectorate. Reference may be made to conclusions recorded in other documents, such as the close-out letter, depending on national procedures.*
Name(s): **Signatures(s):** **Organisation(s):** **Date:** **Distribution of report:**	*The inspection report should be signed and dated by the inspector(s)/assessor(s) who participated in the inspection.*

This may need to be adapted for local use in some Member States where assessment of deficiencies is a separate exercise from the inspection report.

Definition of deficiencies

1. **CRITICAL DEFICIENCY:**

   A deficiency which poses a significant direct risk of causing harm to a recipient patient or to a living donor.

2. **MAJOR DEFICIENCY:**

   A non-critical deficiency:

   which poses an indirect risk to the safety of a donor or a recipient through the procurement and/or distribution of tissues or cells which do not comply with the TE authorisation, process authorisation or the TE's own safety and quality procedures;

   or

which indicates a major deficiency from Directives 2004/23/EC, 2006/17/EC, 2006/86/EC or (EU) 2015/566 or any relevant national regulation;

or

which indicates a failure to carry out satisfactory procedures for release of tissues or cells or a failure on the part of the RP to fulfil his or her legal duties;

or

a combination of several 'other' deficiencies, none of which is major on its own, but which, together, could constitute a major deficiency and should be explained and reported as such.

3. OTHER DEFICIENCY:

A deficiency which cannot be classified as either critical or major, but which indicates a departure from good practice.

Annex 9: Proposed Common Format for a Preparation Process Dossier (PPD)

Preparation Process Dossier

(PPD)

Section A — Tissue Establishment Information

Full name of TE:			
Name of responsible person:			
Postal address of the TE:			
Telephone number:		**Fax number:**	
E-mail address:			

Section B — Preparation Process — General Information

Name of the preparation process:	

Description of the tissues or cells to which this preparation process is	

applied:	

Please give details of any specific additional donor selection or testing requirements that must be applied to the donors of tissues or cells processed in this way.	

Please give details of any specific requirements that must be applied for procurement of tissues or cells processed in this way.	

Please provide a brief description of the preparation process concerned. **(Please attach a flowchart illustrating the process.)**	

Section C — Materials and Equipment

Please list all materials and equipment used in this process, providing details of the supplier in each case.

Reagents or materials that come into contact with the tissues/cells	Specification	Supplier

Equipment	**Specification**	**Supplier**

Section D — Quality Control Testing (including Microbial Testing)

Test	Description of sample (analyte)	Criteria for release

Section E — Process Validation

How have the processing methods applied been validated to demonstrate that they do not render the tissues clinically ineffective or toxic for the recipient?	a) By studies conducted at your TE? YES □ NO □ If yes, please **attach a copy of the validation report.** b) By studies published by others? YES □ NO □ If yes, please **attach copies of the most relevant publications.** c) By retrospective analysis of clinical results? YES □ NO □ If yes, please **attach a summary of the data collected.** d) Others (please specify):……
	e)

If the process is covered by a patent application,	

please provide the patent number.	

If the process includes a sterilisation or viral inactivation step, please provide a brief description of the validation and copies of the virus inactivation studies on which the validation is based.	**Please attach a copy of the validation report.**

Section F — Final Labelling and Accompanying Information Sheet

Please attach here a copy of the final label affixed to the primary packaging of tissues or cells that have been processed using this method. Please attach a copy of the accompanying information sheet supplied to clinical users with the tissues or cells.

Instructions for submission to be inserted by each CA.

Annex 10: Proposed Common Formats for Authorisation Certificates

1. PROPOSED COMMON FORMAT FOR A TISSUE ESTABLISHMENT AUTHORISATION

Details of Tissue Establishment	
Registration/Authorisation number:	
Name of registration-/authorisation-holder:	
Name of TE:	
Address(es) of TE site(s) (all authorised sites should be listed if not covered by separate licences):	
Legally registered address of registration-/authorisation-holder:	

Scope of Authorisation	
Legal basis of authorisation:	
Date of expiry of registration/authorisation (if applicable under national regulations):	
Activities authorised	
Type of tissues or cells	**Prescribed activity (PA)** (Please insert PA code(s) from key below)
Skeletal ☐	
Skin ☐	
Vascular ☐	

Ophthalmic □	
Amniotic membrane □	
Ovarian □	
Testicular □	
Other tissue □ …….....	
Bone marrow □	
PBSC □	
Cord blood □	
Oocytes □	
Spermatozoa □	
Other cells □ ……...	
Embryos □	
Zygotes □	
Other □	

PRESCRIBED ACTIVITY CODES			
Donation: PA1	**Procurement: PA2**	**Testing: PA3**	**Processing: PA4**
Storage: PA5	**Distribution: PA6**	**Import: PA7**	**Export: PA8**

Any restrictions or clarifications relating to the scope of these activities?	

Name of CA officer:	Signature of CA officer:	Date:	CA stamp:

2. COMMON FORMAT FOR A IMPORTING TISSUE ESTABLISHMENT 'AUTHORISATION'

Annex II to Directive (EU) 2015/566

Certificate of Accreditation, Designation, Authorisation or Licence of an Importing Tissue Establishment	
1. Importing Tissue Establishment (ITE) Details	
1.1 Name of ITE	
1.2 EU Tissue Establishment Compendium Code	
1.3 ITE Address and postal address *(if different)*	
1.4 Site of reception of imports *(if different from the above address)*	
1.5 Name of accreditation, designation, authorisation or licence holder	
1.6 Address of accreditation, designation, authorisation or licence holder	
1.7 Telephone number of accreditation, designation, authorisation or licence holder *(optional)*	
1.8 E-mail address of accreditation, designation, authorisation or licence holder *(optional)*	
1.9 URL of ITE website	

2. Scope of Activities							
2.1 Type of Tissues and Cells *(list below using categories of tissues and cells listed in the EU Tissue Establishment Compendium adding rows as necessary)*	Activities in third countries						Import Accreditation, Designation, Authorisation or Licence Status
	Donation	Procurement	Testing	Preservation	Processing	Storage	
	3CS – Third country supplier *SC – Sub-contractor of third country supplier*						*G - Granted* *S- Suspended* *R- Revoked C-Cessation*
2.2 One-off imports							☐
2.3 Product name(s) of imported tissues and cells							
2.4 Any conditions placed on the import or clarifying remarks							
2.5 Third country or countries of procurement *(per tissue and cell import)*							
2.6 Third country or countries in which other activities take place *(if different)*							
2.7 Name and country of third country supplier(s) *(per tissue and cell import)*							
2.8 EU Member States in which imported tissues and cells will be distributed *(if known)*							

3. Competent Authority (CA) Accreditation, Designation, Authorisation or Licence		
3.1 National accreditation, designation, authorisation or licence number		
3.2 Legal basis of accreditation, designation, authorisation or licence		
3.3 Date of expiry of accreditation, designation, authorisation or licence *(if any)*		
3.4 First accreditation, designation, authorisation or licence as ITE or renewal	First time □	Renewal □
3.5 Additional remarks		
3.6 Name of CA		
3.7 Name of CA Officer		
3.8 Signature of CA Officer *(electronic or otherwise)*		
3.9 Date of accreditation, designation, authorisation or licence		
3.10 CA Stamp		

Annex 11: Documents Consulted for Drafting these Guidelines

Documents produced by regulators

Agence de la Biomédecine (ABM) guidance on inspection of centres for assisted conception (draft)

AFSSAPS guidance for tissue and cell bank inspection (Aide-Mémoire for Inspection of Tissue and Cell Banks, 2004; Inspection Guidelines Relating to Procurement of HSC and Mononuclear Blood Cells; Sub-Guidelines Relating to Inspection of Procurement of Cells from Umbilical Cord Blood, 2007)

Belgian competent authority:

- Aide-mémoire for tissue bank inspection, April 2006
- Site master file for tissue and cell banks

National Transplant Centre, Italy (CNT) guidance for tissue bank inspection (Guidelines on the Conduct of Inspections, 2005: Pre-inspection form and skin-bank inspection checklist as an example)

EMEA GMP inspection guidance documents: CoCP (Compilation of Community Procedures) Inspection Conduct (EMEA/INS/GMP/313513/2006) and report writing EMEA/INS/GMP/313539/2006)

EN ISO 14971:2007 Medical devices — Application of risk management to medical devices

FDA Compliance Programme Guidance Manual, 2005

Human Fertilisation and Embryology Authority (HFEA), UK — Tissues and cells for assisted conception (www.hfea.gov.uk)

- information on the system
- pre-inspection questionnaire

Human Tissue Authority (HTA), UK. Inspection Site Visits: Manual for Specialist Assessors (2006) and Guidance for Designated Individuals (2006)

Irish Medicines Board, Aide-Mémoire for Tissue Establishments

Irish Medicines Board, Authorisation of Prescribed Activities carried out in Relation to Human Tissues and Cells (Certificate)

Irish Medicines Board, Points to Note for the Inspection of Reproductive Cells

ISO guidelines for quality and/or environmental management systems auditing (ISO 19011)

Medicines Control Council, Department of Health, RSA, Guidelines for Preparation of Site Master File

Medicines and Healthcare Products Regulatory Agency (MHRA), UK. Consultation on a risk-based inspection programme for good practice inspections

PIC/S Guidance for Blood Establishments, 2004

PIC/S Standard Operating Procedure (pi 026-1 October 2006): Qualification and training of inspectors in the field of human blood, tissues and cells

Documents produced by professional societies or projects

AABB Quality System Assessment Tool, 2006

AATB Tissue Bank Self-Assessment Tool and Audit Report (Star), 2006

EBAA, Inspection Manual of the Eye Bank Association of America, 2005

EQSTB (European Quality System for Tissue Banks — DG SANCO project) — Tissue Bank Audit Guidelines, 2007

JACIE Inspection Manual, 2004

Tissue Bank Evaluation Guidance used by the International Atomic Energy Agency in its reviews of tissue banks worldwide supported by its programme

Annex 12: Abbreviations and Glossary

CA	Competent Authority
EMEA	European Medicines Agency
EU	European Union
GMP	Good Manufacturing Practice
HPC	Haematopoietic Stem Cells
ITE	Importing Tissue Establishment
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICSI	Intracytoplasmic Sperm Injection
ISO	International Organisation for Standardisation
IUI	Intra-Uterine Insemination
IVF	In Vitro Fertilisation
MS	(European Union) Member State
NAT	Nucleic Acid Amplification Technique
PIC/S	Pharmaceutical Inspection Cooperation Scheme
QA	Quality Assurance
RP	Responsible Person
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SOP	Standard Operating Procedure
TE	Tissue Establishment
TED	Tissue Establishment Dossier
3CS	Third Country Supplier

	Definition	**Source**
Audit	Documented review of procedures, records, personnel functions, equipment, materials, facilities and/or vendors in order to evaluate compliance with written SOPs, standards or government laws and regulations,	Adapted from the Council of Europe Guide for Safety and Quality Assurance for Organs, Tissues and Cells for

	conducted by professional peers, internal quality system auditors or certification body auditors	Transplantation, 3rd Edition, Council of Europe Publishing, January 2007
Cells	Individual human cells or a collection of human cells when not bound by any form of connective tissue	Directive 2004/23/EC
Critical	Potentially having an effect on the quality and/or safety of or coming into contact with the cells and tissues	Directive 2006/86/EC
Distribution	Transport and delivery of tissues or cells intended for human applications	Directive 2004/23/EC
Donation	Donating human tissues or cells intended for human applications	Directive 2004/23/EC
Donor	Every human source, whether living or deceased, of human cells or tissues	Directive 2004/23/EC
Expert	Individual with appropriate qualifications and experience to provide technical advice to a CA inspector	Guidelines Drafting Group
Human application	Use of tissues or cells on or in a human recipient/ patient and extra-corporal applications	Directive 2004/23/EC
Organisation responsible for application of human tissues and cells	A healthcare establishment or unit of a hospital or another body which carries out human application	Directive 2006/86/EC
Partner donation	Donation of reproductive cells between a man and a woman who declare that they have an intimate physical relationship	Directive 2006/86/EC
Preservation	Use of chemical means, alterations in environmental conditions or other means during processing to prevent or retard biological or physical deterioration of tissues or cells	Directive 2004/23/EC
Processing	All operations involved in preparation, manipulation, preservation and packaging of tissues or cells intended for human applications	Directive 2004/23/EC
Procurement	A process by which tissues or cells are made available	Directive 2004/23/EC
Procurement organisation	A healthcare establishment or a unit of a hospital or another body that procures	Directive 2006/86/EC

	human tissues and cells and that may not be accredited, designated, authorised or licensed as a tissue establishment	
Quality system	The organisational structure, defined responsibilities, procedures, processes and resources for implementing quality management, including all activities which contribute to quality, directly or indirectly	Directive 2006/86/EC
Reproductive cells	All tissues and cells intended to be used for the purpose of assisted reproduction	Directive 2006/86/EC
Responsible person	Every tissue establishment must designate a responsible person for: ensuring that human tissues and cells intended for human application in the establishment for which that person is responsible are procured, tested, processed, stored and distributed in accordance with the Directives and laws in force in the Member State concerned; providing information to the competent authority or authorities as required; and implementing the requirements of the Directives within the tissue establishment	Directive 2004/23/EC
Serious adverse event	Any untoward occurrence associated with the procurement, testing, processing, storage and distribution of tissues and cells that might lead to transmission of a communicable disease, to death or to life-threatening, disabling or incapacitating conditions for patients or which might result in, or prolong, hospitalisation or morbidity	Directive 2004/23/EC
Serious adverse reaction	An unintended response, including a communicable disease, in the donor or in the recipient associated with the procurement or human application of tissues and cells that is fatal, life-threatening, disabling, incapacitating or which results in, or prolongs, hospitalisation or morbidity	Directive 2004/23/EC
Standard operating procedures	Written instructions describing the steps in a specific process, including the materials and methods to be used and the expected properties of the tissues or cells to be distributed	Adapted from Directive 2006/86/EC
Storage	Maintaining the tissues or cells under appropriate controlled conditions until distribution	Directive 2004/23/EC

Third country	Any country that is not a Member State of the European Union	European Commission: ec.europa.eu
Third party	Any organisation that provides a service to a procurement organisation or a TE on the basis of a contract or written agreement. Includes donor- or tissue-testing laboratories, contract sterilisers and user hospitals which store tissues or cells pending human application	Operational Manual Drafting Group
Tissue	All constituent parts of the human body formed by cells	Directive 2004/23/EC
Tissue establishment	A tissue bank or a unit of a hospital or another body where processing, preservation, storage or distribution of human tissues and cells are undertaken. It may also be responsible for procurement or testing of tissues and cells	Directive 2004/23/EC
Traceability	The ability to locate and identify the tissues/cells during any step from procurement, through processing, testing and storage, to distribution to the recipient or disposal. This also implies the ability to identify the donor and the tissue establishment or the manufacturing facility receiving, processing or storing the tissues/cells and to identify the recipient(s) at the medical facility or facilities applying the tissues/cells to the recipient(s). Traceability also covers the ability to locate and identify all relevant data relating to products and materials coming into contact with those tissues/cells	Directive 2006/86/EC
Validation (or 'qualification' in the case of equipment or environments)	Establishing documented evidence that provides a high degree of assurance that a specific process, piece of equipment or environment will consistently produce tissues or cells meeting its predetermined specifications and quality attributes; a process is validated to evaluate the performance of a system in terms of its effectiveness for its intended use	Directive 2006/86/EC