INSPECTION OF TISSUE AND CELL PROCUREMENT AND TISSUE ESTABLISHMENTS

Guidelines for Competent Authorities

Edition II

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European Union Standards and Training in the Inspection of Tissue Establishments (EUSTITE)

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1.0 Preamble

1.1 The EUSTITE project

These Guidelines have been produced as part of a European Union (EU) funded project entitled 'European Union Standards and Training for the Inspection of Tissue Establishments' (see www.eustite.org). The three year project was launched in December 2006 and co-ordinated by the Italian National Transplant Centre. The project partnership includes representatives of eleven organisations from ten EU Member States (MS) and the World Health Organization (WHO). Ten of the eleven organisations are named by their governments as Competent Authorities (CAs) for the regulation of human tissues and cells for human application. A large number of external experts and key stakeholders are participating in various aspects of the project and have commented on drafts of these guidelines.

1.2 Aim and Scope of these Guidelines

These Guidelines aim to support EU Member States in the implementation of a series of regulatory tasks to be carried out for compliance with the Directives 2004/23/EC, 2006/17/EC and 2006/86/EC. These include:

- The inspection and accreditation, designation, authorisation or licensing of tissue establishments (TEs);
- The authorisation of the conditions for tissue and cell procurement;
- The authorisation of preparation processes for tissues and cells and;
- The regulation of import and export of tissues and cells.

It is intended that the Guidelines should support MS that are establishing such regulatory systems for the first time and also should promote the standardisation of regulatory systems that are already well established in the European Community.

The scope of these guidelines reflects the three related Directives for the quality and safety of human tissues and cells used for transplantation or in assisted conception. Sections of this guideline are relevant for human tissues and cells when used, for example, as a starting material for the manufacture of advanced therapy medicinal products (ATMPs) (i.e. gene therapy, somatic cell therapy or tissue engineering). In these cases the regulatory requirements of donation, procurement and testing from the aforementioned Directives are applicable. A new Regulation 1394/2007/EC, for ATMPs, was published in the O.J.E.C. in December 2007. At this time, MS are advised to liaise with the CA for Medicinal Products to prepare an integrated structure to manage their regulatory responsibilities at the interface of the two healthcare sectors (i.e. site status, inspection practices, certification process, traceability of materials, coding systems).

1.3 Editions I and II

The EUSTITE project plan includes provision for the production of two editions of these Guidelines during the project. The first edition was based on existing guidance in fields related to this, or in this field, in individual Member States and outside the EU. This was submitted to the European Commission in September 2007 as a preliminary document. Since then, it has been distributed to all CAs for tissues and cells in the EU and has been made publicly available on the EUSTITE website. This second edition incorporates comments received on Edition I, as well as a number of findings from different project activities aimed at establishing best practice in the inspection and authorisation of tissue and cell donation, procurement, testing, processing, storage and distribution. These activities included a survey of existing inspection systems (the full report is available on the EUSTITE website) and an exploratory workshop where experts from seventeen

EU MS presented and debated the strengths and weaknesses of different approaches to inspection and authorisation practices.

The full list of documents consulted during the drafting of this document is shown at Annex 11. Section 2.0 of these guidelines is largely based on the Pharmaceutical Inspectorate Co-operation Scheme (PIC/S) document on the qualification and training of Inspectors of blood, tissues and cells. Section 5.0 on the Conduct of Inspections draws heavily on the European Medicines Agency (EMEA) guidance for Good Manufacturing Practice (GMP) inspection, particularly the guidance on Inspection Conduct and Report Writing. The technical annexes have been based, to a significant extent, on national guidance documents, particularly the French Regulator's (AFSSAPS) system, which is the longest established and most well developed in the EU but also drawing from Belgian and Italian guidance and from other guidance in the assisted reproduction field from France and the United Kingdom (UK).

The EUSTITE project is very grateful to the regulatory authorities and professional societies that provided these documents for review.

This second edition was the subject of a public consultation in March 2008. The European Commission aims to present the document to the Tissues and Cells Regulatory Committee for consideration by Competent Authorities (Tissues & Cells) of Member States.

2.0 Qualification and Training of Inspectors

2.1 Education and Experience

In general, Inspectors should either:

a) have the same level of qualification as required by Article 17 of Directive 2004/23/EC for a 'Responsible Person' (RP), or

b) have the necessary education and experience to inspect such a site.

In line with the requirements of Directive 2004/23/EC[1] (Article 17, Responsible Person of a Tissue Establishment), a lead Inspector for tissues or cells shall possess a diploma, certificate or other evidence of formal qualification in the field of medical, biological or pharmaceutical sciences which was awarded on completion of a university course of study or a course recognized as equivalent.

The Inspector shall have practical post-graduate experience in relevant areas of operations within a blood, tissues or cells establishment, or may have appropriate pharmaceutical industry or relevant healthcare experience or regulatory experience of working within a CA that inspects blood establishments or hospital blood banks, medicinal products or tissues and cells establishments. In certain circumstances experience can substitute for academic qualification.

In addition to a sound technical knowledge, the Inspector should possess good interpersonal skills. He/she should be a good communicator, 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.

2.2 Initial Training

In order to obtain a position as Inspector within an Inspectorate, the new employee will have demonstrated that he/she possesses the qualifications and experience necessary to perform the

[1] Directive 2004/23/EC of the European Parliament and of the Council of 31 March 2004 (Official Journal of the European Union L102, 7.4.2004, p.48)

expected functions. In addition, it must be recognised that the skills required to be an Inspector are specialist and initial/induction training is to be provided by the Inspectorate, regardless of qualifications or previous experience.

The initial/induction training should be designed to cover at least the following topics:

- 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, EN);
- National Health systems and tissue and cells organizational structures in the MS;
- National legislation in place in the MS;
- Organisation of national/international regulatory authorities and Inspectorates.

2.3 Specialised Training

As stated above Inspectors will, in general, have a wide range of competency obtained through education, qualification, previous work experience and/or by their complementary training programme. However, it is likely that the Inspector will not have the same level of knowledge in all subjects 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 the Inspector can perform inspections to the required standard.

The following list provides an outline of important subjects in which the Inspector may require training:

- Basic knowledge of processes and equipment used in TEs;
- Basic knowledge of medical devices regulations;
- Design, validation and maintenance of critical environments and equipment;
- Data processing and protection systems;
- Effective communication including conflict management;
- General Principles of transplantation of tissues and cells;
- General hygiene;
- Identification of, and subsequent actions pertaining to, illegal or fraudulent activity;
- Laboratory techniques / *In-vitro* diagnostic tests (screening tests, nucleic acid amplification techniques);
- Principles of tissue and cell application in reproductive medicine;
- Risk Management;
- Specific national guidelines/requirements;
- TE activities (donation, procurement, testing, processing, storage, distribution);
- Transmissible diseases;
- Vigilance and surveillance.

2.4 In-Service Training, Certification and Continuous Development

The in-service training program should include a certain number (to be defined by the Inspectorate) of witnessed inspections. The trainee Inspector should observe an authorised Inspector perform a number of inspections, then participate in a number of inspections and then lead a number of inspections under the supervision of an authorised Inspector. The competency of the trainee must be confirmed and documented by the CA before he/she is authorised to lead inspections.

2.5 Responsibilities

The role of the Inspector is to verify the compliance of the TE with the regulations. The Inspector should be clearly mandated in writing for the specific task. In line with the specific mandate, the Inspector must gather detailed information to allow the CA to decide on accreditation/designation/authorisation/licensing of the TE and, as necessary, to assess tissue and cell processes regarding suitability for their purpose. An inspection is a sampling exercise as Inspectors cannot examine all areas and documentation during an inspection. An Inspector is not responsible for deficiencies that could not be observed during the inspection due to limited time or scope or because certain processes could not be observed taking place during the inspection.

2.6 Use of Experts

When necessary the Inspector may require the assistance of a technical (e.g. in stem cell technology or assisted reproductive technology) or other (e.g. legal or medical) expert for a specific inspection. The expert should have particular knowledge in the field that is under inspection. The role of the expert is not to inspect but to advise the Inspector on technical matters. Steps should be taken to clearly define in formal documents the mission and role of the expert in the team, the confidentiality agreement of the expert and his/her statement about absence of conflict of interest. Experts should be informed of the Inspectorate's policy on the conduct of inspections.

3.0 Inspection Scheduling

The CA should plan the succession of inspections in advance and elaborate a programme. This programme should ensure that the frequency of inspection of individual TEs can be adhered to as planned. Sufficient resources must be identified and made available to ensure the designated programme of inspections can be carried out in an appropriate manner.

Directive 2004/23/EC requires that tissue establishments be inspected at least at two-yearly intervals. It is recommended that a full on-site inspection covering all areas of activity should be performed at least every 4 years. During the interval between 2 full on-site inspections covering all areas, a thematic on-site inspection may be performed which focuses on a particular area or process (perhaps related to previously reported deficiencies or new activities) or alternatively, in the absence of significant changes since the last inspection, a remote (office-based) review of an updated Tissue Establishment Dossier (TED, see Annex 6 for proposed standard format) may be performed.

3.1 Prioritisation for the Scheduling of Routine Inspections

Routine inspections should be scheduled according to documented criteria based on risk assessment. For planning of routine inspections, scheduling criteria should relate to the following indicators:

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

3.2 Additional (Non-Routine) Inspections

An Inspectorate should have the capacity and authority to conduct non-routine inspections in certain circumstances. These inspections might be announced or unannounced.

Announced inspections may be scheduled:

- In response to an adverse event or reaction to allow the CA to review the investigation of the event and/or to verify that the planned corrective actions have been satisfactorily implemented;
- In response to a reported significant modification to the activities previously authorised;
- To investigate specific issues following a request from a CA in another MS or other official authorities in the MS itself.

Unannounced inspections may be scheduled at short notice or without notice. The criteria for conducting unannounced inspections would 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.

3.3 Tools to verify compliance pending (or in the absence of) a site visit

Where the Inspectorate decides, on the basis of a risk assessment, that a site inspection is not required, then an equivalent means should be used to verify that the activities are in compliance with the EU Directives and the National Regulations. Review of an updated TED may be an alternative regulatory approach to performing a site inspection of a TE.

The TE is asked to provide an updated TED describing compliance with the requirements of the Directives and National Regulations (see a proposed format in Annex 6)**.** Where deficiencies are reported, the dossier should be accompanied with an action plan for correction, signed by the Responsible Person and the TE should be obliged to confirm the successful completion of the action plan.

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4.0 Type of Inspection

Different types of inspection may be carried out according to the activities of the TE. They can include system-oriented inspections, tissue or cell specific inspections, preparation process-related inspections and third party inspections. The conduct of inspections may vary according to their objectives and may focus, for example, on the general level of the quality system, the processing of specific tissues or cells or on a specific preparation process.

System-oriented inspections (organisational structure, policies, responsibilities, quality management, personnel, documentation, facilities, equipment, contracts, complaints and recalls, audits, etc.) or **general inspections** (also termed regular, periodic, planned or routine) should be carried out before a TE is accredited, designated, authorised or licensed and periodically afterwards as required. This kind of inspection may also be necessary for a significant variation of the authorisation and if there is a history of deficiencies.

Re-inspections (also termed 'follow-up' or 're-assessment') may be indicated to monitor the corrective actions required during the previous inspection.

Preparation process-related inspections (these could also be 'special' or 'problem' oriented) may be indicated to assess the adherence of the processing to the TED or the Preparation Process Dossier (see Annex 9) and the manner in which the tissue and cell documentation is maintained. It is recommended preparation processes are assessed separately from a system-oriented TE inspection when the process concerned is complex, innovative or unique to that TE. In this case, they should be assessed on the basis of a thorough documentation review before or apart from a TE inspection, using a form such as the Proposed Common Format for a Preparation Process Dossier at Annex 9. This review may then be followed by a Preparation Process-related inspection. This type of inspection is also indicated when complaints and recalls may relate to one type of tissue or cell or one processing procedure (e.g. sterilisation, labelling, etc). These inspections often include evaluation of risk assessments associated with new or changed processes; guidance on the evaluation of risk assessments is provided at Annex 4.

Donor testing and Quality Control Laboratory Inspections: On-site assessment of adherence to good quality control laboratory practice is normally part of this inspection. This may be performed by a CA that is different from the CA responsible for TE inspection, depending on the situation in each MS.

Third Party Inspections: Competent Authorities may consider scheduling inspections of third parties where a risk assessment indicates that it is appropriate. In the following sample situations, inspections of third parties should be considered:

- 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 sterilizing 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 by a third party with the written agreement.

5.0 Conduct of Inspections

The text of this section gives generic guidance on the conduct of any type of inspection. Annexes 1 to 5 provide technical guidance on how to verify compliance with the specific technical requirements in tissue and cell procurement and donor testing (Annex 1), processing, including quality control testing of tissues or cells, storage and distribution (Annex 2), the assessment of preparation processes (Annex 3), the evaluation of risk assessment reports (Annex 4) and import/export (Annex 5).

5.1 Inspection Procedures - Before the Inspection

Once the inspection date has been set, the composition of the team should be decided, taking the type of inspection into consideration. In general, inspections by a single Inspector should be avoided. Where resources allow, the team should be composed of members with different competencies; at least one Inspector should have the same level of competency/education as required by Article 17 of Directive 2004/24/EC for the RP of the TE or have the necessary education and training to inspect the site. Prior to conducting the inspection the team should familiarise itself with the organisation to be inspected. This should include at least:

- Examination of a TED to review initial status with respect to the EU Directives on tissues and cells and any relevant national regulations;
- A review of the tissues and cells prepared and of the processes applied;

- A review of the reports from previous inspections;
- A review of variations (changes) to the TE authorisation;
- Any specific clothing / vaccination requirements to permit entry to the TE;
- A review of the follow-up actions (if any) arising from previous inspections;
- A review of tissue or cell recalls initiated since the previous inspection;
- An examination of relevant Serious Adverse Events or Reactions (SAE and SAR) notified since the previous inspection;
- A review of any national standards or guidelines associated with 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 the examination of the TED in order to ensure that it is discussed during the inspection.

It is recommended the organisation to be inspected be informed in advance of:

- The objectives and the scope of the inspection, in the light of previous inspections, including the inspection of procurement where relevant;
- Identification of the people whose presence is required during the inspection; in cases where particular processes are to be inspected, the people directly responsible for these processes should be present;
- Identification of the inspection team members and their respective roles;
- The date, time and place, where the inspection is to be conducted;
- Identification of the organizational 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 the transmission of the written inspection report;
- The possibility that, where relevant, the inspection results may be shared with other regulators.

5.2 Inspection Procedures - During the Inspection

Inspectors should strive to create a positive atmosphere during the inspection. An Inspector should be aware of his/her influence on decision making processes. The Inspector should answer questions but avoid entering the role of a consultant. However, the task of an Inspector is not entirely limited to the disclosure of faults, deficiencies and discrepancies; he/she should connect an observation with educational and motivating elements. Inspections may disturb the normal work patterns within an inspected organisation. Therefore, Inspectors should take care not to put the tissue or cells at risk, and should carry out their work in a careful and planned way. Inspectors will, while conducting the inspection, have access to confidential information and should handle it with integrity and great care and in compliance with legal requirements for the protection of confidentiality and the requirements for disclosure for the 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 by their regulations to take photos or videos for evidence at the sites, as long as they do not interfere with the process or the quality and safety of the tissues or cells.

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 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 (the plan may be subject to unannounced modifications).

During the opening meeting the Inspection Team should:

- Outline the purpose and scope of the inspection;
- Review the management structure of the organisation (organisational chart);
- Identify some of the documentation which may be required during the inspection;
- Confirm that all information will be treated as confidential;
- Explain whether deficiencies will be notified as they are identified, at daily closing summary meetings or only at 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; in the case of a team conducting the inspection, a separate room will be required for the debriefing meeting of the team.

An immediate rapid site tour following the opening meeting may be of value 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 may be necessary at this stage to observe certain activities that will not be taking place when the area is visited later in the inspection.

5.2.1 Verification of Control of Incoming Tissues and Cells

The person responsible for donor selection should be present at this stage of the inspection. If this person is not the nominated medical registered practitioner, then the nominated medical registered practitioner should ideally be present also. If a separate organisation plays a significant role (e.g. a Transplant Co-ordination Office) they should also be invited to attend. The system should be reviewed in full with particular attention paid to the following aspects:

- Acquisition and documentation of donor medical and behavioural history;
- Donor testing;
- Donor identification and physical examination;
- Donor history review and acceptance/rejection;
- Procurement documentation;
- Procured tissue or cell labelling, packaging and transport;
- Tissue and cell procurement procedure;
- The referral process for potential donors;
- The system for ensuring traceability while protecting confidentiality.

The Inspector should review representative examples of donor documentation of tissues or cells available for distribution, distributed in the last year, those in quarantine and those that have been imported/exported. Whenever possible, the files should be selected by the Inspection Team and should include files for tissues observed in the TE inventory. On occasions it might be necessary to examine files for tissues or cells that have passed their expiry date.

In some cases, it can be useful for the Inspector to cross-check the procurement information collected during the inspection at a TE by a site inspection of a procurement establishment. Technical guidance on the inspection of tissue and cell procurement and donor testing is provided at Annex 1.

5.2.2. Inspection of the facilities

This should include a detailed tour to determine whether the facilities and equipment are of suitable lay-out and design 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, the Inspector follows the logical flow of the starting materials to preliminary storage, through the processing and quality control areas to the storage location for released finished tissues and cells, taking into account the detailed provisions of Directives 2004/23/EC, 2006/17/EC and 2006/86/EC. Sometimes it is appropriate to concentrate effort in one department of the organisation if there are special problems or requirements. Relevant service areas should be considered, e.g. water, steam, ventilation systems and engineering support.

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

5.2.3 Review of documentation

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

A general system-orientated inspection will normally, in order to assess compliance with the TED, include examination of documentation relating to:

- Job descriptions and the role of the RP;
- Training of staff including initial / induction training and re-training plans and competency assessment;
- Document control, including maintenance (e.g. change control) of standard operating procedures (SOPs);
- Validation (processes) and qualification (equipment, facilities);
- Preventative maintenance programmes (equipment and facilities);
- Selection of suppliers and contracts with suppliers;
- Third party contracting;
- Internal auditing system / self-inspection / corrective and preventive actions;
- Management of complaints, non-conformities, Serious Adverse Reactions (SAR), Serious Adverse Events (SAE), recalls;
- Data handling, confidentiality;
- Import / export.

Operations contracted out and the responsibilities of the different parties should be clearly identified. The contract between the contract giver and the contract acceptor should be examined for compliance with the national regulations that transpose Directives 2004/23/EC, 2006/17/EC and 2006/86/EC.

The procedure for recording and reviewing SAEs and SARs as well as the system for recalling distributed tissues and cells from within and outside the MS should be examined during the inspection. Any reports of SARs and SAEs 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 Inspector, a review of the Audit / Self Inspection Schedule for the previous year to ensure satisfactory completion of audits can be useful. This can be followed up by checking the corrective and preventive action log at the times that audits / self inspections were performed to ensure that suitable actions have been taken.

Procedures for the control of tissue and cell import or export (where relevant) should be reviewed and documentation relating to individual cases of import and export should be examined. Technical guidance on the inspection of import and export is given at Annex 5.

A process-related inspection will normally, in order to assess compliance with the TED, include examination of the specific documentation relating to one or several completed or incomplete processes of a specified tissue or cell preparation including:

- Traceability, tracking (including the donor and tissue/cell coding system in place);
- 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;
- Packing, labelling;
- Distribution.

Technical guidance on the inspection of processing, storage and distribution is provided at Annex 2.

5.2.4 Final Meeting

When the inspection has been completed, the Inspector should summarize the findings in the final meeting with representatives of the organisation, normally the RP and Quality Manager and any officials 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 SOP, provided to the organisation in written form (a form is provided at Annex 7 that could be used for this purpose). An indication should be given verbally of the seriousness of 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 they so wish, 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 actions at the earliest possible date. Deficiencies should be reported with reference to the national laws that represent the transposition of the three EU Directives on tissues and cells. In the case of serious deficiencies presenting an immediate risk to the health and safety of patients, the Inspectorate should delegate to the Inspectors the authority to request the immediate quarantine and/or cessation of supply of the implicated human tissues or cells and, where relevant, their recall. The relevant CA SOPs shall be followed in these special circumstances.

5.2.5 Inspection Notes

Inspection reports should be based on notes taken during the inspection and these should be managed according to the practices specified by the CA. An Inspection Observations Form is provided at Annex 7 which could be used to document observations during the inspection.

5.3 Inspection Procedures - After the Inspection

A written inspection report should describe the scope and observations arising from the inspection. A proposed standard format is shown at Annex 8 which includes a standard classification of deficiencies. The inspection findings may be extracted from this report for sending to the TE in a letter or the entire report may be sent to the TE, depending on the CA's internal procedures.

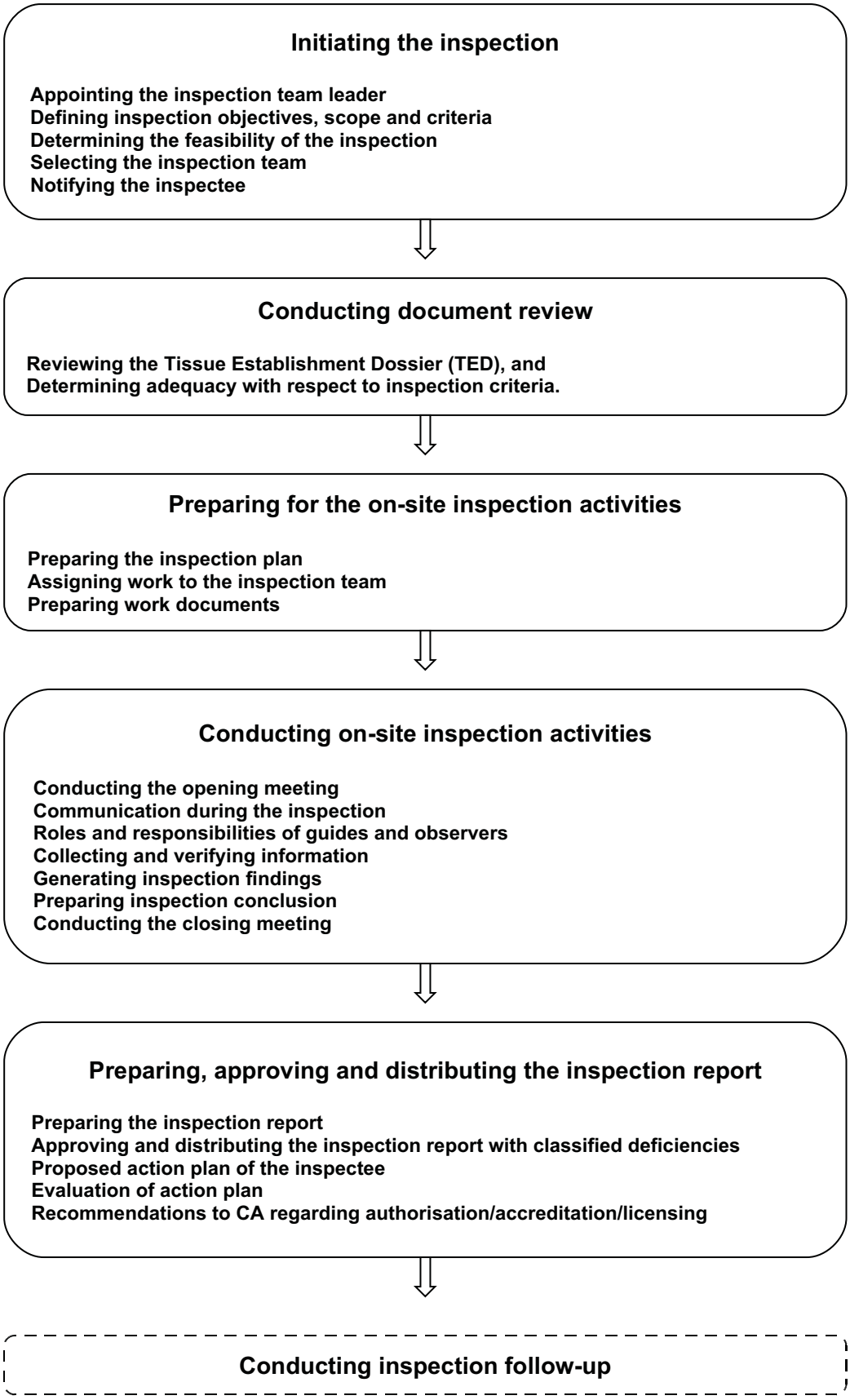
The report should contain a reference to the TED with any corrections to the TED noted from the inspection, a description of the inspection itself and the Inspector's observations and conclusions.

The conclusions should clearly identify deficiencies, classifying them as critical, major or other (according to the definitions given at the end of Annex 8). This is usually done at the Inspectorate to ensure consistency with other inspections. A date should be defined by which the TE should submit proposals and a time schedule for rectifying the deficiencies outlined in the report (action plan). Once it is received, the Inspectors should evaluate the proposed action plan and, on that basis, make a recommendation to the authorising CA for accreditation / designation / authorisation / licensing with a clear statement of whether or not the TE complies with the national laws that represent the transposition of 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 regarding corrective actions before making an authorisation recommendation. The action taken by the CA will depend upon the nature and the extent of deficiency(s) and the adequacy of the corrective action plan, in the context of the EU Directives and the CA's broad knowledge of existing practices related to all types of TEs.

A format for a TE authorisation certificate is proposed in accordance with Directive 2004/23/EC, Directive 2006/17/EC and 2006/86/EC respectively (Annex 10). Tissue Establishments must be accredited, designated, authorised or licensed by a CA in accordance with Article 6 of Directive 2004/23/EC for the purpose of the activities carried out. This format could facilitate construction of the public CA registry for TEs, as required by Directive 2004/23/EC (Article 10) and support the provision of information to the database functionality created by EUROCET (www.eurocet.org). The proposed format includes only the minimal information that should always be included in the certificate and in the CA's register of authorised TEs. Further information could be added, according to the CA's own requirements, that would not be published in the public registry, but would be part of the national registry of the CA.

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

Figure 1 summarises the process of inspection.


Initiating the inspection
Appointing the inspection team leader
Defining inspection objectives, scope and criteria
Determining the feasibility of the inspection
Selecting the inspection team
Notifying the inspectee
Conducting document review
Reviewing the Tissue Establishment Dossier (TED), and
Determining adequacy with respect to inspection criteria.
Preparing for the on-site inspection activities
Preparing the inspection plan
Assigning work to the inspection team
Preparing work documents
Conducting on-site inspection activities
Conducting the opening meeting
Communication during the inspection
Roles and responsibilities of guides and observers
Collecting and verifying information
Generating inspection findings
Preparing inspection conclusion
Conducting the closing meeting
Preparing, approving and distributing the inspection report
Preparing the inspection report
Approving and distributing the inspection report with classified deficiencies
Proposed action plan of the inspectee
Evaluation of action plan
Recommendations to CA regarding authorisation/accreditation/licensing
Conducting inspection follow-up

6.0 Evaluation of the Inspection System

Competent Authorities should perform an evaluation of their inspection systems according to their specified procedures. Information that may assist the development of the evaluation programme is outlined below:

6.1 System performance (the 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 certified/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 process authorisation application to final report.

6.2 Inspector performance

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

- Number of inspections performed per Inspector per year;
- Number of centres certified/authorised/licensed per Inspector per year (if applicable);
- Average time per Inspector from inspection to final report;
- Number of processes assessed (where applicable) per Inspector per year;
- Number of processes authorised (where applicable) per Inspector per year.

6.3 Inspector qualification process

The system should include periodic evaluation of the Inspector performance e.g. by joint inspection visits with senior or specialist Inspectors 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 determined action is carried out.

Note: these indicators should be adjusted to take into account the type, size and complexity of the TEs inspected.

Annex 1: Procurement and Donor Testing - Verification of Technical Requirements

General considerations for an inspection of the procurement establishment

The verification of donation and procurement practices may be performed indirectly by the auditing of these services at the TE or directly by a specific site inspection of the organisation where these activities take place. The aim of this inspection is to review at least the following:

- The organisation in place for procurement (personnel, training and qualification)
- donor (or donor family or legal representative) consent in accordance with national regulations; records should indicate how the consent has been obtained;
- Donor records should be examined for evidence and completeness of the donor history, physical examination, testing and haemodilution evaluation;
- Procurement process: SOPs, records;
- The facilities where the retrieval of tissues or cells is carried out (dedicated area for deceased donors, procedures for decontamination and cleaning of the room, aseptic technique used, SOPs in place to avoid cross contamination, etc);
- The instruments used for procurement (single use or if reusable: decontamination and sterilization by validated techniques);
- Procedures in place for obtaining blood samples for serological and/or NAT testing of donors, identification and handling of the samples, assessment of the laboratory tests;
- Packaging and labelling;
- The area where the tissues or cells are temporarily stored before shipment and transportation to TE (including temperature control);
- System of traceability used (e.g. coding of the procured tissues or cells);
- Documentation that accompanies the tissues or cells to the TE;
- Any adverse reactions or events that have occurred during procurement from living donors.

The Inspector must check that donor selection and evaluation were performed by trained personnel according to SOPs and described in detail in records. There shall be SOPs for the verification of donor identity, donor/donor family or legal representative consent (as required by national regulations), assessment of selection criteria for deceased (beating and non heart beating) and living donors and assessment of laboratory tests required. These SOPs should reflect the requirements of Directive 2006/17/EC and/or the equivalent national regulation in full. There shall be proof of all consents required by local legislation and the regulations.

Donor selection and screening records shall be reviewed by the Inspector for compliance with the requirements regarding: donor identity, consent details, medical history requirements, assessment of selection criteria and behavioural risks, detailed physical examination and assessment of laboratory testing results. For living donors, there must be evidence that a face-to-face interview was conducted during which a questionnaire based on the requirements of Directive 2006/17/EC was completed. For deceased donors, there must be evidence of which alternative sources of information were used. The Inspector must check that the cause, time and circumstances of death are recorded. For deceased donors, it should be confirmed that national/local requirements for the confirmation of death have been complied with before tissue procurement began. The Inspector must review the medical donor file to confirm that adequate information is sought to allow the application of the exclusion criteria in Annex 1 of Directive 2006/17/EC. Therefore, he or she has to select a number of donor records at random to examine the evidence that all the exclusion criteria have been appropriately investigated and applied. This review should confirm that:

- The donor's behavioural history (with relevance to increased risk of disease transmission) has been checked;
- Any signs that may be sufficient in themselves to exclude the donor are detected, with particular attention to tumours, infections, risk factors for transmissible diseases, trauma to the donor's body or scars from recent or old operations;
- All the biological tests results have been done accordingly with the EU directive or any relevant national regulation (for deceased donors, blood samples should be obtained prior to death or if not possible, within 24 hours of death. For living donors, blood samples should be obtained at the time of donation, or if not possible, within 7 days post donation);
- Appropriate investigations are carried out to ensure that blood samples used for testing are not diluted by prior transfusions or infusions so as to render the test result invalid.

Donor record

For each donor, there must be a record containing:

(a) The donor identification (first name, family name and date of birth — if a mother and child are involved in the donation, 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, laboratory test results, and the results of 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 of 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 and an assessment of the risk of transmission of inherited conditions known to be present in the family must be carried out, after consent is obtained
(j) For 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 shall be in compliance with data protection legislation, and shall be legible and permanent. Data protection and confidentiality measures shall be in place according to Article 14 of Directive 2004/23/EC.

Retrieval conditions

The Inspector must check that tissue and cell procurement are performed in appropriate rooms by educated and trained personnel, using qualified equipment and methods described in detail in SOPs. For living donors, procurement must occur in an environment that ensures their health, safety and privacy. All equipment and instruments used shall be qualified, and sterilized between procurements, according to a validated method. Sterile single-use instruments shall be used

whenever possible. Aseptic technique shall be used throughout the procurement procedure. Samples for microbiological testing or other quality control tests must be taken where applicable according to the SOPs in place.

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

(a) The identification, name and address of the TE to receive the cells/tissues;
(b) Donor identification data (including how and by whom the donor was identified);
(c) Description and identification of procured tissues and cells (including samples for testing, where appropriate);
(d) Identification of the person who is responsible for the procurement session, including a signature;
(e) Date, time (where relevant, start and end) and location of procurement and 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) Date time and identification of the person who obtained samples for biological tests
(g) For deceased donors, conditions under which the cadaver was kept: refrigerated (or not), time of start and end of refrigeration;
(h) ID/batch numbers of reagents and transport solutions used.

For cadaveric donors, the report must also contain 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.

The date and time of procurement may be included, where possible.

Transportation

The Inspector must check written procedures to verify that transport and packaging conditions are validated and in place. He or she should examine a few packaging containers and their labels and evaluate their suitability, check for evidence of their sterility (primary packaging) at the time of use and whether the integrity and required storage and/or transport conditions of the tissues or cells are maintained.

Donor Testing

Verification of compliance with the testing requirements of Directive 2006/17/EC should be performed by either:

- an inspection visit to the testing laboratory, or
- by examination of certification/accreditation for each test performed. The latter should include evidence that the tests used were validated and that the laboratories were accredited, designated, authorised or licensed by the CA or authorities to perform those tests.

If the TE itself does not perform the testing, it must enter into a contract with a laboratory which is accredited, designated, authorised or licensed by the CA or appropriate authorities. If the laboratory is authorised by a CA other than the CA for tissues and cells, the Inspectors performing the TE inspection should request a copy of the authorisation certificate or verify with the other CA that the appropriate authorisation for tissue and cell donor screening is in place. TEs must confirm compliance of contracted testing laboratories with the requirements, and the maintenance of the requirements, through participation in external quality assessment schemes, wherever possible. The means by which this confirmation was established should be reviewed during the TE inspection.

During the inspection, the Inspector must:

- Check if the testing described in procedures is in compliance with the requirements of the national regulations that transpose Directive 2006/17/EC;
- Examine the testing carried out in practice and a representative number of tissue or cell files to verify that it is in compliance with the national regulation transposing 2006/17/EC / as stated in the TED.

Annex 2: Inspection of Processing, Storage and Distribution during a Tissue Establishment Inspection Visit

Requirements for processing, storage and distribution are detailed in Directive 2006/86/EC, Annex II.

The Inspector(s) must check whether the information provided in the TED is accurate and if the processes applied are compatible with the equipment and facilities used by the TE.

The following methods are recommended for the verification of compliance with these requirements:

1.0 Review of documents

- Review of standard operating procedures;
- Review of processing records;
- Review of the results of the classification of processing areas (including a review of the documented evidence that supports the reported classification);
- Review of procedures and data to ensure and demonstrate maintenance of the classification (including particle counting, environmental microbial sampling, procedures for entering the area including gowning procedures);
- Review of procedures to ensure avoidance of cross-contamination;
- Review of procedures to ensure appropriate restricted access and protection of confidential data;
- The following documents, as a minimum, should be requested for review:
  - One maintenance and calibration record for a critical piece of storage equipment selected by the inspection team;
  - One example of a document showing the authorisation of tissue or cell for transfer from quarantine to distribution.

2.0 Interviews with staff

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

3.0 Observations and examinations

- Inspection of the storage area – particular attention should be paid to:
  - Control of relevant physical conditions (e.g. temperature, 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 that is used for tissue and cell identification and traceability at each step of the process (e.g. coding, labelling, IT system);
  - Biohazard waste (restricted area, security, handling, packaging and labelling, etc);
- Inspection of the processing (controlled) area – particular attention should be paid to:
  - Flow of staff, starting 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;
- Examination of labels including the label on the final tissue or cell package;
- Examination of storage temperature monitoring records;

- Challenge of traceability by selecting finished tissues and cells available for distribution and requesting information on:
    - The donor history;
    - The date and time the processing was carried out;
    - The identity of the person who carried it out;
    - Which batches/lots of reagents or additives were used, with expiration dates;
    - Which equipment was used, if applicable its status of maintenance, qualification;
    - Specifications for all steps of the processes;
    - Which environmental conditions the tissue or cell were exposed to (including storage locations);
    - What type of microbiology testing was performed and their results (including the results of microbiological control of cell based products as prescribed by the European Pharmacopeia or by alternative control that is acceptable to the CA);
    - Who released the tissue or cell and on what basis.
- Review of documentation of requests and of tissue or cells distributed;
- Examination of package insert information issued with tissues or cells;
- Review of agreements with third parties who may distribute tissue or cells on behalf of the TE;
- Examination of non-conformities registered within the TE and the corrective and preventive actions taken (by random sampling);
- Review of any serious adverse event or reaction reports and the associated corrective actions.

Annex 3: Assessment of Preparation Processes

Requirements for the authorisation of tissue and cell preparation processes are detailed in Directive 2006/86/EC, article 4 and annex II.

It is recommended that preparation processes are assessed separately from the TE inspection visit where the process is complex, innovative or unique to that TE. In this case, they should be assessed on the basis of a thorough documentation review before or apart from an inspection using a form such as the Proposed Common Format for a Preparation Process Dossier at Annex 9. The findings of such a review can be confirmed during a subsequent on-site inspection. Processes which are simple, well established and widely applied can be adequately assessed during a TE inspection visit.

Processes which are listed in Annex 1 of the Advanced Therapy Medicinal Products Regulation (1394/2007/EC) are not regarded as substantially manipulation and are typically performed by TEs; this guidance therefore applies to the assessment of those processes. The processes are as follows (though this list is not exhaustive):

- Cutting;
- Grinding;
- Shaping;
- Centrifugation;
- Soaking in antibiotic or antimicrobial solutions;
- Sterilization;
- Irradiation;
- Cell separation, concentration or purification;
- Filtering;
- Lyophilisation;
- Freezing;
- Cryopreservation;
- Vitrification.

Substantially manipulated tissues and cells are regulated by the Advanced Therapy Medicinal Products (ATMP) Regulation.

Where it is judged that a non-ATMP process is complex, innovative or unique and should therefore be assessed separately from a TE inspection, it should be performed by a minimum of one assessor or Inspector and, unless the Assessor/Inspector is technically 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 (for requirements regarding confidentiality and conflicts of interests, see 2.6).

When an innovative process or a significant modification of a process is implemented, the TE should submit a revised PPD (or a new addendum to the PPD) for the authorisation of the new process.

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 or for studies demonstrating clinical effectiveness.

It should be noted that Directive 2006/86/EC allows for validation studies to be based on any of the following:

- Studies performed by the establishment itself;
- Data from published studies, or;
- For well established processing procedures, retrospective evaluation of the clinical results for tissues and cells supplied by the establishment.

Where validation is based on studies performed by the establishment itself, reports should include at least the following elements:

- 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 validation acceptance or rejection by the Quality Manager or the RP.

Where validation is based on data from published studies, the publications should be made available for review. In this case, the TE 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(ies). Where specific steps have been modified or adapted, separate validation should confirm that these changes have not invalidated the method. There should be a signed declaration of validation acceptance or rejection by the Quality Manager or the RP.

Where validation is based on retrospective evaluation of the clinical results for tissues or cells supplied by the establishment (for well established processing procedures) evidence should be provided of the number of tissue or cell grafts implanted following processing by the method under consideration and the period of time during which these implantations occurred. It should be demonstrated that, where a vigilance system was already in place at the time, clinical users were informed of the procedure for reporting adverse reactions. There should be a signed declaration of validation acceptance or rejection by the Quality Manager or the RP.

Evaluation of Risk Assessment Reports

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

Annex 4: Evaluation of Risk Assessment Reports

Within Directives 2004/23/EC, 2006/17/EC and 2006/86/EC, there are several legal requirements for performing a risk assessment when managing tissues or cells for human use. Their 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 may be achieved by the application of new techniques or revised procedures which are updated with the best scientific advice.

Inspection programmes should verify a TE fulfils their duty to perform risk assessments to determine the disposition of stored tissues and cells when new donor selection or testing criteria are introduced or any significantly modified processing step which enhances quality or safety is introduced (Annex II, Directive 2006/86/EC). This approach is of more significance when the inspection process identifies tissues or cells which were earlier donated, tested and stored according to pre-existing national regulations and/or professional practices and which may 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.

Inspectors should verify that a risk assessment performed at a TE did adopt a methodical approach to the scientific evaluation of the related elements. This is in order to allow an appropriate decision to be reached. All risk assessment plans should be documented with the following elements:

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

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

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

The scope of a management plan should identify (e.g. a flowchart) and describe the principal activities of the TE and the circumstances to which the different phases of the plan are applicable. All elements of the risk management process should be linked to the authorised/licensed activities of

the TE. Its detail should be related to the known and perceived risks associated with the different types of tissue or cells. It could be a separate document or integrated within the Quality System.

Informative guidance on the application and tools for risk assessment are provided in the International Standard for the Risk Management to Medical Devices (EN ISO 14971) and the Harmonised Tripartite Guideline for Quality Risk Management (ICHQ9).

Annex 5: Import/Export – Verification of Technical Requirements

Importation by Tissue Establishments

Where a TE is importing from third countries, inspection of this activity should address:

- The reason for the choice to import;
- The nature of the agreement with the exporting party, i.e. whether it covers a routine supply arrangement or a 'one-off' arrangement.

Routine importation

In this case, the inspection should include examination of the documentation relating to the review by the importing TE of the equivalence of quality and safety systems at the exporting establishment. This should cover both of the following:

- Documentation describing the general quality and safety system at the exporting establishment: organisational chart, staff training, facilities, processing methods, validation studies, system of traceability, licenses and accreditation, etc.
- Documentation relating to the review of safety and quality of individual despatches of tissues or cells: confirmation of type of tests performed and their results, donor suitability, tissue or cells description, transportation arrangements etc.

'One-off' importation

In this case, the inspection should include examination of the importing TE's documented evaluation of the safety and quality of the tissue or cells imported.

Third Country inspections by EU Competent Authorities

The EU Directives give responsibility to TEs to verify that organisations from which they import tissues or cells work to standards of quality and safety that are equivalent to those detailed in the Directives. However, in some cases, CAs may consider it necessary to go to a supplier of tissues or cells in a third country and to conduct an inspection. The criteria for conducting such an inspection might include:

- Where multiple TEs are importing from a single third country establishment;
- Where a high volume of tissues or cells are being imported from a single third country establishment;
- Where there is evidence of poor performance by an establishment in a third country that is exporting to a TE in the EU;
- Where an SAR/SAE has been associated with the tissue or cells concerned.

Third country inspections should be conducted following the guidance in the general section of this document. The Inspectorate of the country should be notified about the inspection and should be invited to accompany the Inspector and should also receive a copy of the report.

Where one MS CA approved importation from a particular third country establishment, it is recommended that the process on which the approval was based and the report be shared among other MS CAs.

Authorisation of Import involving 'Direct Distribution'

Direct distribution is defined in Directive 2004/23/EC and involves distribution of tissues or cells directly from a collection centre to a transplant centre without processing of the material. As there is no involvement of a TE, in the case of direct distribution from a third country, the CA is responsible for authorising the import and may apply more stringent criteria than those detailed in the Directives. Direct distribution applies primarily to haematopoietic stem cells and in some cases to tissues and cells for assisted conception. In some cases, the authorisation request will be made by the clinical centre that will apply the material and in some cases by a National or Regional Transplant Registry. In these cases, the review by the Transplant Physician or the Transplant Registry should include:

- Rationale for import;
- Documentation from the registry or the transplant centre on equivalence of safety and quality (including any certificates/authorisations in place);
- Where information is lacking or full compliance with the EU Directives cannot be evidenced but the Transplant Centre wishes to proceed, the documented risk assessment performed by the Transplant Centre (or Registry) should be reviewed.

In general, import and delivery to the Transplant or Fertility Centre should be permitted in quarantine and the authorisation should be provided rapidly, taking into consideration the short life and unique nature of the tissue or cells and the condition of the intended recipient.

Tissue and Cell Export by Tissue Establishments

The requirements for export of tissues and cells outside the European Union are included in Article 9 of Directive 2004/23/EC.

The inspection of a TE that is exporting tissues to a third country must include 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 are different to those included in the tissues and cells Directives. A representative number of records should be reviewed to ensure that equivalent standards for safety and quality are applied to these tissues or cells. 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.

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			
TE Mailing Address			
Telephone Number		**Fax Number**	
Email address:			

Activity Summary: Please tick the relevant boxes to indicate the activities carried out on site:

PRESCRIBED ACTIVITY:	**TISSUES:**	**PROCESSES** (including contracted processes):
Donation	Skeletal	Cutting/grinding/shaping
Procurement	Skin	Soaking in antibiotic or antimicrobial solutions
Testing	Vascular	Sterilisation (not by irradiation)
Processing	Corneas	Irradiation
Storage	Amniotic Membrane	Cell separation, concentration, purification
Distribution	Other	Filtering
Import	……..	Lyophilisation (Freeze-drying)
Export	……..	Freezing
		Cryopreservation
	CELLS:	Vitrification
	Bone marrow	Drying
	PBSC	Demineralisation
	Cord blood	Storage in Organ culture medium
	Reproductive cells	4^0C storage
	Other cells	Glycerolisation (high concentration)
	……	Volume reduction
	……	Centrifugation
		Sperm preparation (including washing and centrifugation)
		IVF without ICSI
		IVF with ICSI
		Other
		…….
		…….

Reference number/code of the Competent Authority processing authorisation (if available)	

Section B – Activity - Details

Please attach a flow-chart which describes the full activity of the TE

Does the TE conduct procurement?	**YES/NO** (If no, indicate which procurement organisations provide tissues/cells to the TE)
Does the TE conduct donor testing?	**YES/NO** (If no, indicate which organisation(s) conducts testing of the tissue/cell donors)
Types of tissues/cells received by the TE (from own procurements or procurements by others) (please list here or attach separately)	
Number of donors from whom tissue/cells were received at the TE in the previous year	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 separately)	

How have the processing methods applied been validated to demonstrate that they do not render the tissue clinically ineffective or toxic for the recipient? (not necessary to complete if 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 separately)
Types of finished tissues/cells distributed by the TE (please list here or attach separately)	
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 tissue 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 tissue/cells and name(s) the country(ies) of origin and the name(s) of TE(s)
Does the TE import tissues/cells from outside the EU for distribution?	**YES/NO** (if yes, indicate which type of tissue/cells and name(s) the country(ies) of origin and the name(s) of TE(s)

Number of tissue or cell units (individual packages, bags, straws or vials) distributed by the TE for human application in the previous year	

Section C – Personnel

Name of Responsible Person as defined in Directive 2004/23/EC **(Please attach a brief curriculum vitae)**	
Name of TE Director (if different from above) **(Please attach a brief curriculum vitae)**	
Name of Medical Director (if different from above) **(Please attach a brief curriculum vitae)**	
Name of Quality System Manager **(Please attach a brief curriculum vitae)**	
Name of Processing Manager (where relevant) **(Please attach a brief curriculum vitae)**	
Total number of staff	

Provide a functional organisational chart which identifies roles and reporting relationships **(Insert in the space provided or attach separately).**
Please indicate in the organisational chart how many people are working in 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 environmental classification, where relevant.
(Please attach a plan of the area, the rooms (numbered), their dedication as well as personnel, tissue or cells, 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 distribution)?	**YES/NO** (If yes, indicate which steps and name the organisation that acts as the third party). Please provide copies of relevant agreements

Section G – Transportation

Please describe the arrangements in place for the transport of each type of tissues or cells from procurement to the TE	
Please describe the arrangements in place for the transport of each type of tissue 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 the reporting and management of SAE and SAR	

Section I – Quality 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 professional society	**YES/NO** (If yes, please give details of when and by whom and **add certification number**)

Section J – Signature and Date

Signature of Responsible Person **Date:**	

Section K – Instructions for the Submission of this Form

This form should be submitted as an initial application for accreditation/designation/authorisation/licensing by the Competent Authority for tissues and cells. It should be re-submitted when significant changes in activity, staffing or processes applied have taken place or when there are significant changes to any of the attached documents.
Changes considered to be significant include:

- **change of Responsible Person**
- **use of new equipment for an authorised process**
- **a new contract is signed with new subcontractors, or a new agreement with a collecting centre**
- **transfer of one or all of the activities to new premises**
- **cessation of activities or site closure**
- **a new IT system is implemented**

Each CA to insert relevant instructions for submission

Annex 7 – Proposed Optional 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» «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 ☐

n°	Observation	Comments

Facilities/Premises

Assessed during this inspection ☐	Not assessed during this inspection ☐

n°	Observation	Comments

Materials and Equipment

Assessed during this inspection ☐	Not assessed during this inspection ☐

n°	Observation	Comments

Quality Management System

Assessed during this inspection ☐	Not assessed during this inspection ☐

n°	Observation	Comments

Donor Selection, Donor Testing and Procurement

Assessed during this inspection ☐	Not assessed during this inspection ☐

n°	Observation	Comments

Processing, storage and distribution

Assessed during this inspection ☐	Not assessed during this inspection ☐

n°	Observation	Comments

Quality Control

Assessed during this inspection ☐	Not assessed during this inspection ☐

n°	Observation	Comments

Distribution Outside MS, Import and Export

Assessed during this inspection ☐	Not assessed during this inspection ☐

n°	Observation	Comments

Traceability

Assessed during this inspection ☐	Not assessed during this inspection ☐

n°	Observation	Comments

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

n°	Observation	Comments

Other

n°	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.:		
Inspected Site(s):	*Name and full address of the inspected site.*	
Activity Summary:	Please tick the relevant boxes to indicate the activities carried out on site:	
PRESCRIBED ACTIVITY: Donation Procurement Testing Processing Storage Distribution Import Export	**TISSUES:** Skeletal Skin Vascular Corneas Amniotic Membrane Other …….. …….. **CELLS:** Bone marrow PBSC Cord blood Reproductive cells Other cells …… ……	**PROCESSES** (including contracted processes): Cutting/grinding/shaping Soaking in antibiotic or antimicrobial solutions Sterilisation (not by irradiation) Irradiation Cell separation, concentration, purification Filtering Lyophilisation (Freeze-drying) Freezing Cryopreservation Vitrification Drying Demineralisation Storage in Organ culture medium 4^0C storage Glycerolisation (high concentration) Volume reduction Centrifugation Sperm preparation (including washing and centrifugation) IVF without ICSI IVF with ICSI Other ……. …….
Inspection date(s): Inspector(s):	*Date(s), month, year* *Name(s) of the Inspector(s)* *Name(s) of Expert / Assessor (if applicable)* *Name(s) of the Competent Authority(ies)*	
Reference to Regulations against which the inspection is conducted:		

Brief Report of the Inspection Activities Undertaken

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

Inspector findings relevant to the inspection including deficiencies This section can link the findings to the deficiencies and be used to explain classification.	
Requirements for procurement and donor testing, as detailed in Directive 2006/17/EC	
Selection criteria for donors of tissues and/or cells as referred to in Article 3(a) and 3 (b) 2006/17/EC	*Describe findings for each type of donor (deceased, living, partner (direct use or indirect use), non-partner)*
Laboratory tests required for donors as referred to in Article 4(1)and 4 (2) 2006/17/EC	
Cell and/or tissue donation and procurement procedures	
Reception at the TE as referred to in Article 5 in 2006/17/EC	
Requirements for accreditation, designation, authorisation or licensing of tissue establishments as referred to in Article 3 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 tissue 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 data set to be kept as required in Article 9 2006/86/EC	*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 of TED; date of TED*
Annexes Attached:	*List of 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 and the relevant reference to the national laws that transpose the EU Directives should be mentioned.* *All deficiencies found should be listed even if corrective action was carried out immediately.* *The TE should be asked to inform the Inspectorate about the proposed time schedule for corrections and on progress.* *Deficiencies should be classified according to 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, within the scope of the inspection, the TE operates in accordance with the national laws that transpose the EU Directives 2006/17 & 86/EC provided, where relevant, that appropriate corrective actions are implemented and mention any other item to alert requesting authority. 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)/assessors having participated in the inspection.*

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

Definition of Significant 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 tissue 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 EU Directive 2004/23/EC, 2006/17 & 86/EC or any other relevant national regulation;

   or

   which indicates a failure to carry out satisfactory procedures for release of tissue or cells or a failure of the RP to fulfil his legal duties.

   or

   a combination of several "other" **deficiencies**, none of which on their own may be major, but which may together represent 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			
TE Mailing Address			
Telephone Number		**Fax Number**	
Email 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	
Detail any specific additional donor selection or testing requirements that must be applied to the donors of tissues or cells processed in this way	
Detail any specific procurement requirements that must be applied for the procurement of tissues or cells processed in this way	
Please provide a brief description of the preparation process concerned (Attach a flow-chart that describes the process)	

Section C – Materials and Equipment

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

Reagents or Materials that come in contact with the tissues/cells	Specification	Supplier
Equipment	**Specification**	**Supplier**

Section D – Quality Control Testing (including microbial testing)

Test	Sample (analyte) Description	Criteria for Release

Section E – Process Validation

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

If the process is the subject of a patent application please provide 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 applied to the primary packaging of tissues or cells that have been processed using this method. Please attach a copy of the accompanying information sheet that is supplied to the clinical user with the tissues or cells.

Instructions for Submission to be inserted by each CA

Annex 10: Proposed Common Format for an Authorisation Certificate

Proposed Common Format for a Tissue Establishment Authorisation

Tissue Establishment Details	
Registration/Authorisation number	
Name of registation/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 according to national regulations)	
Activities Authorised: Please tick the relevant boxes to indicate the prescribed activities authorised to be carried out on site:	
Donation Procurement Testing Processing Storage Distribution Import Export	**TISSUES:** Skeletal Skin Vascular Corneas Amniotic Membrane Other …….. …….. **CELLS:** Bone marrow PBSC Cord blood Reproductive cells Other cells …… ……
Any restrictions or clarifying remarks related to the scope of these activities?	

Name of CA Officer	Signature of CA Officer	Date	CA Stamp

Annex 11 - Documents Consulted in the Development of these Guidelines

Documents developed by Regulators

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

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

Belgian Competent Authority documents
- Aide-memoire 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 the 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 their 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 Memoire 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 the 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 developed 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 - SANCO project) - Tissue Bank Audit Guidelines, 2007

JACIE Inspection Manual, 2004

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

Annex 12: Abbreviations and Glossary

CA	Competent Authority
EMEA	European Medicines Agency
EU	European Union
GMP	Good Manufacturing Practice
HPC	Haematopoietic stem cells
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICSI	Intracytoplasmic sperm injection
ISO	International Standards Organisation
IUI	Intra uterine insemination
IVF	In-vitro Fertilisation
MS	European Union Member State
NAT	Nucleic acid amplification technique
PIC/S	Pharmaceutical Inspection Co-operation Scheme
QA	Quality Assurance
RP	Responsible Person
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SOP	Standard Operating Procedure
TED	Tissue Establishment Dossier

	Definition	**Source**
Audit	Documented review of procedures, records, personnel functions, equipment, materials, facilities, and/or vendors in order to evaluate adherence to written SOPs, standards, or government laws and regulations, conducted by professional peers, internal quality system auditors or certification body auditors.	Adapted from the Council of Europe Guide for Safety and Quality Assurance for Organs, Tissue and Cells for 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 having contact with the cells and tissues	Directive 2006/86/EC
Distribution	transportation 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	the use of tissues or cells on or in a human recipient / patient and extra-corporal applications	Directive 2004/23/EC
Inspection	on-site assessment/control of compliance with the EU tissues and cells directives principles and national regulations performed by officials of Community Competent Authorities	Adapted from the Compilation of Community Procedures on inspections and exchange of information published on behalf of the European Commission by EMEA (European Medicines

		Agency). Conduct of Inspections of Pharmaceutical Manufacturers
Organisation responsible for application of human tissues and cells.	a health care establishment or a unit of a hospital or another body which carries out human application	Directive 2006/86/EC
Partner donation	means the donation of reproductive cells between a man and a woman who declare that they have an intimate physical relationship	Directive 2006/86/EC
Processing	all operations involved in the preparation, manipulation, preservation and packaging of tissues or cells intended for human applications	Directive 2004/23/EC
Preservation	The 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
Procurement	a process by which tissue or cells are made available	Directive 2004/23/EC
Procurement organisation	a health care establishment or a unit of a hospital or another body that undertakes the procurement of human tissues and cells and that may not be accredited, designated, authorised or licensed as a tissue establishment	Directive 2006/86/EC
Quality system	means the organisational structure, defined responsibilities, procedures, processes, and resources for implementing quality management and includes 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
Serious adverse event	any untoward occurrence associated with the procurement, testing, processing, storage and distribution of tissues and cells that might lead to the transmission of a communicable disease, to death or 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 tissue or cells under appropriate controlled conditions until distribution	Directive 2004/23/EC
Third country	any country that is not a Member State of the EU	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	Guidelines drafting group

	contract or written agreement. Includes donor or tissue testing laboratories, contract sterilisers and user hospitals which store tissues or cells pending human application.	
Tissue	means all constituent parts of the human body formed by cells	Directive 2004/23/EC
Tissue establishment	means a tissue bank or a unit of a hospital or another body where activities of 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 tissue/cell during any step from procurement, through processing, testing and storage, to distribution to the recipient or disposal, which also implies the ability to identify the donor and the tissue establishment or the manufacturing facility receiving, processing or storing the tissue/cells, and the ability to identify the recipient(s) at the medical facility/facilities applying the tissue/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 tissue or cells meeting its predetermined specifications and quality attributes; a process is validated to evaluate the performance of a system with regard to its effectiveness based on intended use	Directive 2006/86/EC

Annex 13 – Drafting Group and Contributing Organisations

Drafting Group

Name	Organisation
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Project Partners

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Federal Ministry of Health, Family and Youth, Austria
Bulgarian Executive Agency for Transplantation
Danish Medicines Agency
Irish Medicines Board
Agence de la Biomédecine, France
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National Centre for Tissue and Cell Banking, Poland
Human Fertilisation and Embryology Authority, UK
World Health Organization, Switzerland

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Centro Nazionale Trapianti, Italy
Danish Medicines Agency
Executive Agency for Transplantation, Bulgaria
Federal Agency for Medicines and Health Products, Belgium
Human Fertilisation and Embryology Authority, UK
Human Tissue Authority, UK
Irish Medicines Board
Latvian Health Statistics and Medical Technologies State Agency
National Institute for Public Health and the Environment, The Netherlands
Swedish National Board of Health and Welfare
University Hospital, Bratislava, Slovakia
U.S. FDA CBER, Office of Compliance and Biologics Quality