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Good Tissue Practices

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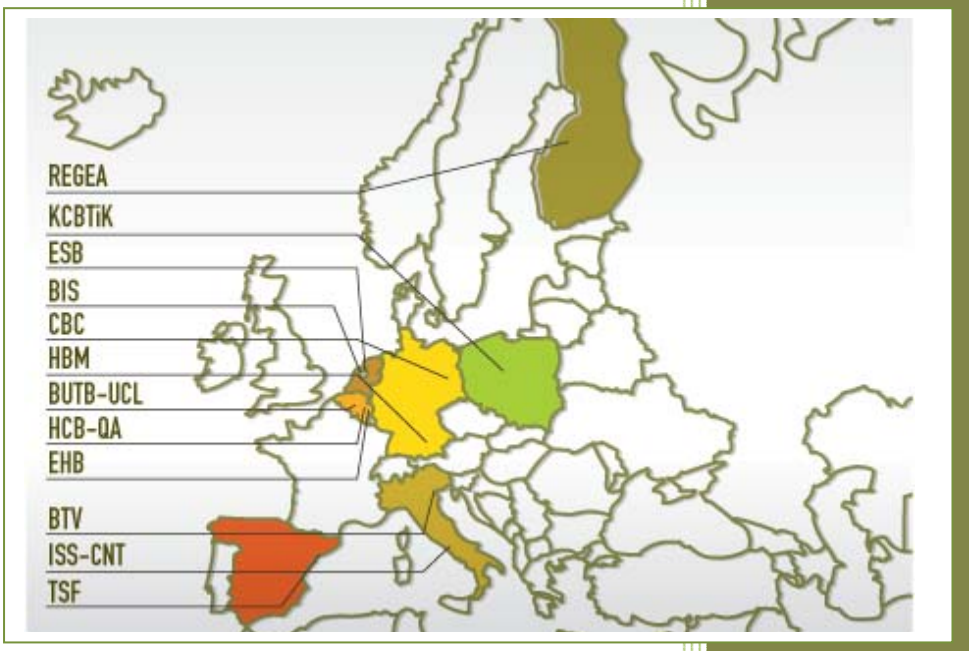

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1. DONOR SELECTION

1.1Medical and social evaluation

1. The evaluation of the donor should contain all the necessary medical and social information to assess the presences of the following aspects:

a) General contraindications concerning the safety of all donated tissue as stated in Directive 2004/23/EC Annex I;

b) Additional safety related contraindications that are the result of risk assessments that arise from health risks related to processing, donor population characteristics, emerging infectious diseases, or other relevant factors;

c) Tissue specific contraindications that involve the quality of the donated tissue.

2. The final determination of the criteria for exclusion for tissue donation is the responsibility of the responsible person, in consultation with a medical advisor or medical advisory committee, if needed. A list of mandatory and optional contraindications could be:

Medical evaluation	
Weight and height NTS (pre screening)	If no exact weight and height are known, an estimate will suffice.
Active systemic. infections and vaccinations NTS (pre screening)	This includes all systemic infections (bacterial, viral, parasitical, prions). Various circumstances are possible including: 1. An infection at the time of death. Please report: ▪ the type of infection ▪ lab results ▪ whether cultures have been taken, including (provisional) results ▪ antibiotic treatment, including duration and effectiveness of the treatment and if any, the results of the treatment (e.g. fever-free period). 2. Suspicion of a systemic infection without supportive diagnostics. Please report the symptoms on which the suspicions are based. 3. In case clinical signs are not highly suspect for an infection but infection cannot be ruled out, please report as such. 4. Systemic infections of which the patient has been cured, but the cause is still (possibly latent) present (e.g. polio, hepatitis B-C, syphilis) 5. Report vaccinations given with live attenuated virus, such as polio, mumps, measles, rubella and post exposure rabies vaccinations. The criteria used to assess whether sepsis is present are in accordance with the internationally guidelines.
Clinical evidence or suspicion of neurodegenerative diseases with unknown aetiology, or other disorders possibly	The following apply: ▪ All non-vascular or unexplained forms of dementia, such as Alzheimer's disease; ▪ ALS, multiple sclerosis, Parkinson ▪ variant CJD or risk factors for prion disease such as familial CJD, the use of growth hormone and stay in the UK during 1980-1996.

caused by prions NTS (pre screening)	
Haematological malignancies or other haematological disorders NTS (pre screening)	All lymphoproliferative, myeloproliferative and other haemapoetic disorders, such as leukemia, Morbus Kahler, non-Hodgkin disease, polycythemia vera and aplastic anaemia.
Other malignancies. *Mind: Malignancies are no general CI* NTS (pre screening)	Present at time of death or in the medical history.
Infection or signs of infection	All, also local, infections or signs of infection such as lab results, positive cultures, infiltration on X-thorax. Treatment with antibiotics? *Infections can be a tissue specific contraindication.*
Bone marrow suppression due to medication in the last 3 months	Medication administered within three months before death with a proven bone marrow depression. Mention which medication, indication, dose and last lab. results (Hb, leucocytes and platelets)
Chronic use of corticosteroids	Relevant in case of chronic use for more than 6 weeks. Provide details on indication, dosage and duration of use. *Use of corticosteroids can be a tissue specific contra-indication.*
Other medication	Please report all other medications that have been used.
Infusions and transfusions within the previous 48 hours	Only relevant if given for blood loss. Please report type and quantity of all infused fluids (blood products, colloids, crystalloids, plasma replacement, plasma expanders etc.), as well how much and time of the infusions/transfusions
Social evaluation	
Presence of risk factors for HIV, HTLV, Hepatitis B or C	This group includes donors belonging to known risk groups (either directly or through their sexual partners): - Persons who have used non-medical drugs intranasal in the last 5 years. - Persons who have ever injected non-medical drugs (intravenous, intramuscular or subcutaneous). - Persons with haemophilia or related clotting disorders who have received human-derived clotting factor concentrates before 1987. - Men who have had sex with another man in the preceding 5 years. - Men and women who have engaged in sex in exchange for money or drugs in the preceding 5 years. - Persons emigrated from countries where transfer of HIV infection through heterosexual contacts plays an important role in the spreading of the HIV virus, like countries in South East Asia, Caribbean and in countries in Africa below the Sahara. Unless person has been in the Netherlands longer than 1 year and in that time has not been back to an endemic region. - Persons that, in the past 6 months, had sexual contact with persons of one of the above mentioned groups or were sexual partners of persons who are infected with HIV, HTLV or hepatitis C or B or who are suspected thereof. - Persons that, in the preceding 6 months, were exposed to (possibly) infected blood via accidental percutaneous puncture or through contact with an open wound and non-intact skin or mucous membrane. - Persons who are diagnosed or treated for SOA in past 6 months. - Children of 18 months or younger born to mothers with risk of HIV,

	or children from these mothers who were breastfed. - Tattoo: if the donor has had a tattoo, piercing or needle accident in the previous 6 months, there may be a reason for not accepting. Please contact the BIS doctor on duty for evaluation. We do not accept piercings made with the use of shared needles or genital piercings. - Persons of have jaundice of unknown but possibly infectious origin. - Persons who are in "Close contact" with another individual with infectious hepatitis, such as shared household (kitchen and toilet) or sexual partner during the last 6 months. Intermittenthaemodialysis
Intoxications	Includes alcohol abuse, drug abuse and long term exposure to heavy metals such as lead, mercury, chromium, arsenic, pesticides. Nicotine abuse is not relevant.
Risk of tropical diseases, for example as a result of travel.	Report risk for emerging diseases contracted during travel to foreign countries, such as SARS, Avian Flu, Malaria, Yellow fever etc. Mention: which country, duration and date period of stay, vaccinations. If unknown report as such.
Travel / Visit to the United Kingdom	Report if known whether duration of stay was longer than 6 months and between January 1980 and December 1996. If unknown report as such.

3. For every potential donor, anamnestic data must be obtained from the available relevant sources, such as the donor (living) treating physician, general practitioner, next of kin or other people who knew the donor well (deceased) and / or the donor's medical record included in the donor file.

4. When questioning donors or their relatives it must be established that the phrasing of the questions is understood by the answering person.

1.2. Physical evaluation of cadaveric donors

1. The evaluation of the cadaveric donor should include a physical examination to detect signs:

a) that are in themselves sufficient to the exclude the donor; or
b) that may be an indication for further investigations; or
c) are a contraindication for donation, when assessed in light of the donor’s medical and social history.

2. The physical examination has to be performed by trained personnel, in a working area with sufficient light, and under the condition that the entire body surface is easy accessible for examination by the retrieval staff.

3. A written report on the findings during the physical examination should minimally consist of a check list of specific signs that have to be look for. Findings should also be drawn on a diagram of the body.

4. An example is given of a list of signs and their associated contraindications that indicate a (potential) cause for rejection of the donor for donation.

1.3 General impression

Describe the degree of care of the donor

Inspection of the skin	**Description (including localisation, dimensions type/aspect, signs of infection)**
Jaundice	❒ No ❒ Yes
Tattoos / piercings	❒ No ❒ Yes Old / new
Non-therapeutic needle wounds	❒ No ❒ Yes
Skin abnormalities / petechiae	❒ No ❒ Yes
Traumas / wounds / scars	❒ No ❒ Yes Old / new
Lines (arterial / venous)	❒ No ❒ Yes

1.3 Specific inspection

Head / neck	
Abnormalities of eyes/sclera	❒ No ❒ Yes ❒ Already enucleated
Abnormalities of oral cavity	
Other facial abn. (e.g. infectious)	❒ No ❒ Yes
Pathological lymph nodes (>1 cm or abnormal consistency)	❒ No ❒ Yes
Abn. of the ears (e.g. CSF, blood)	❒ No ❒Yes
Torso & extremities	
Enlarged liver / spider naevi	❒ No ❒ Yes
Pathological lymph nodes (>1 cm or abnormal consistency)	❒ No ❒ Yes
Indications for auto-immune/ connective tissue conditions	❒ No ❒ Yes
Fractures	❒ No ❒ Yes
Genitalia	
Abnormalities of the genitalia	❒ No ❒ Yes
Inspection of the rear side of the body	
Skin abnormalities	❒ No ❒ Yes
Peri-anal abnormalities	❒ No ❒ Yes

2. RECOVERY AND PROCESSING ENVIRONMENTS

2.1 Microbiological safety of tissue

2.1.1 Selecting the appropriate air quality for processing

The TE can apply this FMEA risk assessment method to evaluate the risk of microbiological contamination of the tissue during processing. Microbes on the final tissue may originate from the donor or have been added during the processing steps. Donor selection is carried out to reduce the risk of transmission of inherent bacteria from the donor to the patient. Recovery of the tissue must be carried out as described in these good tissue practices, to minimize the risk of contamination. During further processing, no microbes should be added to the tissues and therefore processing steps are performed in a safety cabinet (Class A air quality) placed in a room with at least Class D air quality (minimum according to Directive 2006/86/EC) using sterile materials and equipment.

It is noted that skin has an intrinsic flora of commensal microbes. Several measures can be taken to remove this flora (washing with betadine, chlorohexidine or other antimicrobials).

The TE can use this FMEA tool to demonstrate the measures in place to reduce the risk of contamination during processing are acceptable. The following risk tool for defining the quality of the processing area can be used to evaluate each particular tissue and process.

Factor	1	3	5	7	9	Score
Risk that contaminants will not be detected in the tissue due to limitations of the sampling method	10% destructive testing in compliance with European Pharmacopea.	Tissues preserved in culture medium (contamination visible)	A biopsy of tissue tested from every individual graft processed	Pieces of tissue tested for each process run (< 1% of the run)	Swabbing of final tissue	
Risk of contamination during manipulation*	Tissue exposed to processing environment for < 1 hr	Tissue exposed to processing environment for 1-3 hr	Tissue exposed to processing environment for 3-5 hr	Tissue exposed to processing environment for 5-7 hr	Tissue exposed to processing environment for > 7hr	
Use of antimicrobials	Agents with validated reduction of microbial contamination (by >3 logs)	Agents with published evidence of effective reduction of microbial contamination (85% glycerol	Validated antibiotic Cocktail treatment	Fluid storage and conditions in final container not promoting microbial	Fluid storage and conditions promoting microbial growth (temperature > 10 °C)	

		for skin processing)		growth (e.g. low temperature)	
Risk of transfer of contaminants at transplantation *a. Type of tissue*	Acellular	No vital cells	Vital cells but no vessels	Vital cells and minor vessels	Fully vascular with vital cells
Risk of transfer of contaminants at transplantation *b. Type of use*	Temporary superficial coverage < 3 weeks	Durable superficial coverage > 3 weeks	Durable implant in a poorly vascularised site	Small durable implant in a well vascularised site	Large durable implant in a well vascularised site

*To estimate this risk it is advised to perform 'sham' tissue manipulation sessions in the processing area using tissue containers with only the media used for the microbiology tests ('media fill').

The use of antimicrobials is a measure to reduce the risk of contamination during processing. Also, the risk of growth of micro-organisms in a graft stored in medium at 33°C is higher compared to a graft stored in the freezer.

To specify an appropriate air quality on the basis of the scores in the risk tool, the following is recommended as guidance:

< 20:	Class A with D background
20-29:	Class A with C background
> 30:	Class A with B background.

Examples:

2.1.2 Skin in 85% glycerol

Factor	**1**	**3**	**5**	**7**	**9**	**score**
Risk that contaminants will not be detected in the tissue due to limitations of sampling method	10% destructive testing in compliance with European Pharmacopea.	Tissues preserved in culture medium (contamination visible)	A biopsy of tissue tested from every individual graft processed	Pieces of tissue tested for each process run (< 1% of the run)	Swabbing of final tissue	5
Risk of contamination during manipulation*	Tissue exposed to the processing environment for < 1 hr	Tissue exposed to the processing environment for 1-3 hr	Tissue exposed to the processing environment for 3-5 hr	Tissue exposed to the processing environment for 5-7 hr	Tissue exposed to the processing environment for > 7hr	5
Use of antimicrobials	Agents with validated reduction of microbial	Agents with published evidence of	Validated antibiotic Cocktail treatment	Fluid storage and conditions in final	Fluid storage and conditions promoting	3

	contaminatio n (by >3 logs)	effective reduction of microbial contaminati on (85% glycerol for skin processing)		container not promoting microbial growth (e.g. low temperature)	microbial growth (temperatu re > 10 °C)	
Risk of transfer of contaminants at transplantatio n a. Type of tissue	Acellular	No vital cells	Vital cells but no vessels	Vital cells and minor vessels	Fully vascular with vital cells	3
Risk of transfer of contaminants at transplantatio n b. Type of use	Temporary superficial coverage < 3 weeks	Durable superficial coverage > 3 weeks	Durable implant in a poorly vascularised site	Small durable implant in a well vascularised site	Large durable implant in a well vascularise d site	1

2.1.2.1 Rationale

1. Sampling method: in contrast to other tissues, skin tissue is inherently colonised by micro-organisms. Therefore it is more reliable to test pieces of skin than the collection and storage media and it is feasible to take pieces of tissue from every sheet of skin in the final container into the sample for the microbiology test. For most TE, 10% of the tissue to be used for testing is considered too great a loss of transplantable tissue.

2. Processing of a batch of skin takes at least 3 hours (amount of cm2 per donor varies but 2.000cm2 is generally retrieved).

3. Glycerol at high concentrations inactivates different species of bacteria, see references 1-3. A validation study has not been done so far.

4a. Glycerol 85% preservation results in non-vital skin with intact morphology (ref 4).

4b. Skin is used to provide temporary coverage of a wound, as a biological dressing, not as an implant.

5. Total score is 17 for 85% glycerol preserved skin, therefore processing in A with a D background would be indicated as adequate. However, it is noted that this analysis would need to be carried out by each centre, considering its own protocols and risk reduction measures.

.1.3. Heart valves, cryopreserved

Factor	**1**	**3**	**5**	**7**	**9**	**score**
Risk that contaminants will not be detected in the tissue due to limitations of the sampling method	10% destructive testing in compliance with European Pharmacopea.	Tissues preserved in culture medium (contamination visible)	A biopsy of tissue tested from every individual graft processed	Pieces of tissue tested for each process run (< 1% of the run)	Swabbing of final tissue	7
Risk of contamination during manipulation*	Tissue exposed to the processing environment for < 1 hr	Tissue exposed to the processing environment for 1-3 hr	Tissue exposed to the processing environment for 3-5 hr	Tissue exposed to the processing environment for 5-7 hr	Tissue exposed to the processing environment for > 7hr	5
Use of antimicrobials	Agents with validated reduction of microbial contamination (by >3 logs)	Agents with published evidence of effective reduction of microbial contamination (85% glycerol for skin processing)	Validated antibiotic Cocktail treatment	Fluid storage and conditions in final container not promoting microbial growth (e.g. low temperature)	Fluid storage and conditions promoting microbial growth (temperature > 10 °C)	5
Risk of transfer of contaminants at transplantation a. Type of tissue	Acellular	No vital cells	Vital cells but no vessels	Vital cells and minor vessels	Fully vascular with vital cells	7
Risk of transfer of contaminants at transplantation b. Type of use	Temporary superficial coverage < 3 weeks	Durable superficial coverage > 3 weeks	Durable implant in a poorly vascularised site	Small durable implant in a well vascularised site	Large durable implant in a well vascularised site	7

2.1.3.1 Rationale

1. Sampling method: the heart valves may be contaminated during recovery, thus at the surface of the tissue. Therefore, testing of the collection and storage media is important.

Pieces of tissue for testing must be taken without compromising the function, therefore samples are not representative.

2. In general, the processing takes 3 - 5 hours including dissection, evaluation and antibiotic treatment and final packaging.

3. Only an antibiotic cocktail can be used for decontamination as more robust treatments would compromise the viability of the tissue.

4a. Vital cells may be present as well as small vessels.

4b. Heart valves are used as durable implant, relatively small but implanted in a highly vascularised central site.

5 Total score is 31 for cryo-preserved heart valves, therefore processing in an A with a B background would be indicated. However, it is noted that this analysis would need to be carried out by each centre, considering its own protocols and risk reduction measures.

3.TISSUE SPECIFIC QUALITY CRITERIA

3.1.Amniotic membrane

a) Absence of transmissible disease agents and malignant cells
b) Integrity (to provide barrier function)
c) Accurately sized pieces and clean edges

3.2.Bone

a) Absence of transmissible disease agents and malignant cells (Sterile if labelled as such)
b) Biomechanical strength (for weight-bearing applications)
c) Graft morphological specifications (e.g. length, particle size, porosity)
d) Osteoinductivity if demineralised
e) Residual moisture if lyophilized (maximum to be defined)

3.3.Cornea

a) Endothelial characteristics (cell density and morphology)
b) Morphology and integrity of the cornea layers
c) Free visual area and diameter of corneal button
d) No evidence of microbiological growth or malignant cells

3.4.Heart valves

a) Absence of transmissible disease agents and malignant cells
b) Functional competence
c) Good morphology (no fissures, congenital defects, no/minimal calcification etc.)

d) Anatomical suitability; accurate length of conduit and diameter of annulus

e) Tissue matrix structure intact

f) Biomechanical strength

3.5.Meniscus

a) Absence of transmissible disease agents and malignant cells (Sterile if labelled as such)

b) Biomechanical strength

c) Graft morphological specifications (e.g. surface integrity, no abnormalities/defects, accurate dimensions)

3.6.Skin

a) Absence of transmissible disease agents and malignant cells

b) Correct thickness

c) Integrity (to provide barrier function)

d) Accurately sized pieces and clean edges

e) Cell viability (optional, depending on the intended application)

f) Sterile if labelled as such

3.7.Tendons

a) Absence of transmissible disease agents and malignant cells (Sterile if labelled as such)

b) Biomechanical strength and elasticity

c) Graft morphological specifications (e.g. surface integrity, no abnormalities/defects, accurate dimensions)

d) Residual moisture if lyophilized (maximum to be defined)

4. RISK MANAGEMENT

4.1 Introduction

This chapter on Risk management presents an overview of a formal risk management process for application in a Tissue Establishment (TE). The aim of the chapter is not to introduce new guidance; all the information is available within already existing legislation and guidelines. The objective is to provide practical directions for the performance of a risk analysis in a Tissue Establishment.

It is possible and acceptable within Good Manufacturing Practices (GMP) for risk assessment to be informal, using empirical tools and experience to estimate and mitigate risks instead of a formal method. This type of risk assessment is not included in this GTP Risk management chapter.

The ultimate goal of the risk management process in Tissue Establishments is to enhance the quality and safety of tissues for the patient. However, the level of effort, formality and documentation of the risk management process should be commensurate with the level of risk.

4.2 What does risk management provide for your organisation?

Risk management processes are a **regulatory requirement** for health care products, including pharmaceutical products. It assures **product quality, reliability and safety** and it results in a situation where **residual risk is within manageable** or acceptable limits. Although tissues for transplantation are not exactly a pharmaceutical product, risk management may be a good tool for identification and controlling of associated risks.

Validation is another fundamental element of quality management on a GMP-GTP basis. Risk assessment is the appropriate tool to support decision-making regarding the specific validations that a tissue establishment needs to perform. The risk assessment will highlight the critical points in the process allowing the development of an appropriate validation plan.

Validations in GMP focus mainly on the critical steps in the production and test phase, in the context of pharmaceuticals for example. A similar approach should be taken in planning a risk assessment in order to define a tissue establishment validation programme.

Inspectors, and other authorities, are increasingly looking to see the evidence behind certain decisions on quality and safety. Risk assessments serve as **documentation of the rationale** for decisions. They support making better and more informed decisions on improving organisations and processes.

Moreover, regulators and authorities are more assured of an organisation's ability to act competently in response to potential risks when they see evidence of a robust quality risk management system.

Risk assessments highlight where action should be taken to achieve improvements and where control can be eased in the context of a risk based rationale. The degree of control should reflect the degree of risk associated with each activity. Risk assessment is a useful tool for prioritisation of corrective action plans. For example, a list of corrective actions following an internal audit can be prioritised for action by an assessment of the quality risk associated with each non-compliance.

4.3 What is risk management?

The basis of all risk management processes consists of **three principles**:

a) Risk assessment
b) Risk control
c) Risk review

4.4 Relevant definitions in the risk management process

Harm	Damage to health of recipient, including the damage that can occur from loss of product quality or availability (loss of tissue, damage for the donor)
Hazard	The potential source of harm
Risk assessment	contains risk identification, risk analysis and risk evaluation.
Risk analysis	The estimation of the risk associated with the identified hazards
Risk evaluation	The comparison of the estimated risk to given risk criteria, using a quantative or qualitative scale, to determine the significance of the risk
Risk control	contains risk reduction or risk acceptance
Risk review	contains an evaluation or review after a period of time to assess the measures taken and define if the identified risks are reduced effectiveley

Based upon the 3 principles of risk management, the definition of risk management could be stated as follows:

‘Risk management is the overall quality management process by which risks are identified, evaluated, controlled, monitored and reviewed.’

Severity = the degree of harm

Probability/occurrence/possibility = the likely rate of occurrence

Risk = severity x probability (x detectability)

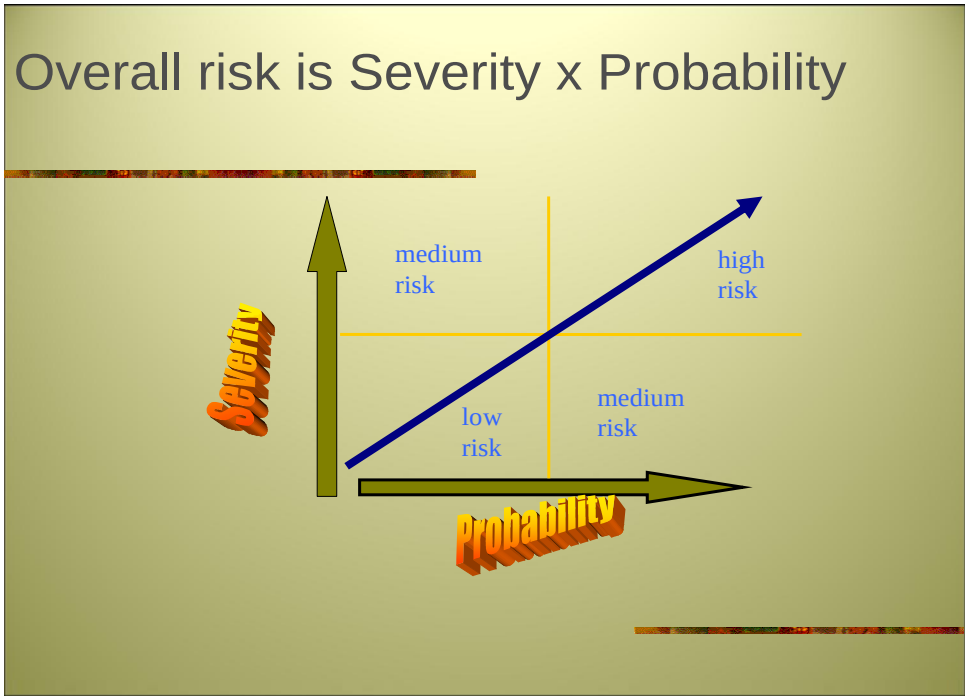

Figure 1 Schematic overview of risk

Figure 2 presents a schematic overview of all steps taken in a typical risk management process. The tools for risk management and the communication on the risk management process are important factors in the risk management process and are therefore drawn on the sides of the process, to underline their mutual dependency.

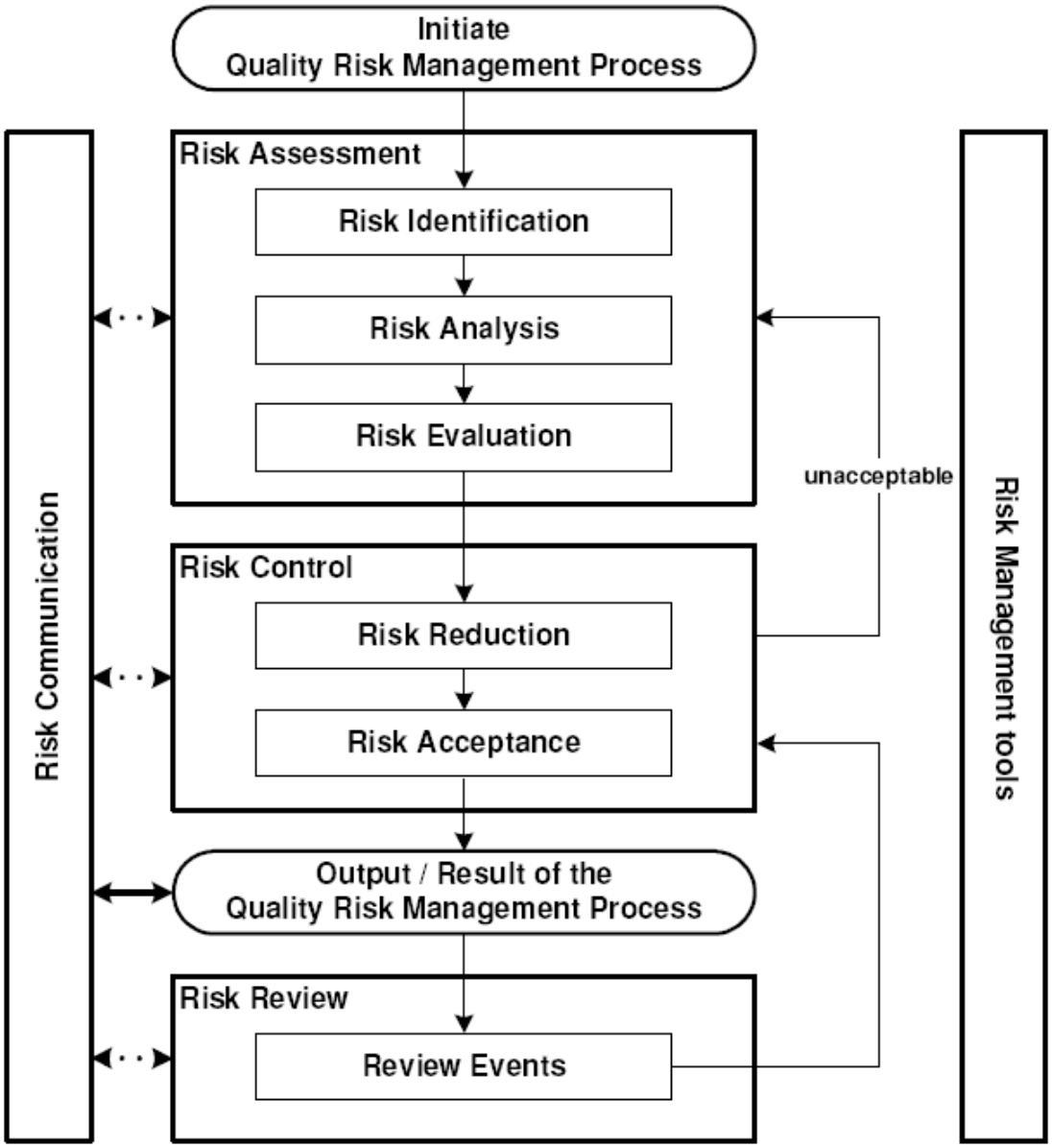

Figure 2: Overview of a typical quality risk management process (source: GMP annex 20)

Figure 3 represents the risk management process in another graphic and more simplified way and is adapted from ISO 14971.

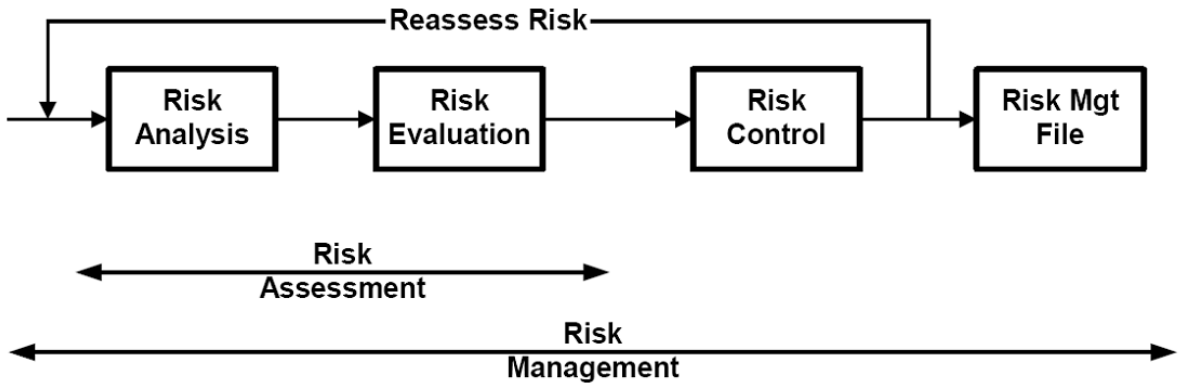

Figure 3: Overview of the risk management process (source ISO 14791)

4.5 Description of the phases in the risk management process

The next paragraph describes more into detail which steps are to be taken in the risk management process.

Risk management can be performed in all (primary) processes of tissue establishments.
It can be used for distribution, storage, recovery but also for medical risk assessment in the donorscreening process.

Risk management is best performed by a **team** consisting of at least:

- one or more process owner(s)
- quality assurance manager

If the risk management process should spread over more than one process, there should be participants of all involved processes present.

To initiate a risk management process, choose a process in which you would like to perform a risk assessment or define a problem description for your risk management process. For example: distribution of tissues by courrier in your country (process) or how can we organise our procurement checklist so that it will be followed precisely by the recoveryteams and will protect the safety and quality of the explants or how we can reduce the risks during

processing Some of these examples will be used in the training model of this GTP, to clarify the risk management process.

4.6 Risk assessment

4.6.1Risk identification

To identify risks first potential hazards should be identified. Think freely and think of worst case scenerario's: what might go wrong?

List all potential hazards that might possibly arise in e.g. your distribution process, and do not stop and think of measures already taken.

Input for your list could be generated from your quality system, for example:

a) Non conformities that were registered and categorized in the last 1 or 2 years;
b) Customer/user comments/feedback registered and categorized in the last 1 or 2 years;
c) Incidents of near incidents that have been identified;
d) Serious adverse reactions or events that occurred in the last 1 or 2 years;
e) Outcome of internal / external audits or inspections;
f) Other quality registrations;
g) Experience and 'gut feeling' of employees in the process;
h) Other sources from your organisation.

4.6.2 Risk analysis

In the phase of risk analysis you score the potential hazards and their consequences so you will define the risks. Scoring can be quantitative or qualitative, but both are defined beforehand. The occurrence (also called likelihood or probability) and the severity play an important role in this phase. In some risk management processes the factor of detectability is included in the assessment.

Varying methods are available to help you rate the risks, which will be elaborated on in this chapter.

4.6.2.1 Rating of potential hazards/assessment of risks.

After having listed the potential hazards, investigate the consequences of the potential hazards. Helpful questions to identify the consequences are:

a) What would be the worst possible outcome from this hazard? What harm could come from this hazard? How severe would the harm be?
b) How likely is it that the potential hazard will occur and will cause the harm?

4.6.3 Risk evaluation

After identifying and analysing hazards, the risk evaluation phase confirms the risks that have been raised by considering the criteria in the first two phases. Take into account the measures that are already in place to diminish the risks. Is the risk acceptable or must something be done to reduce it?

4.6.4 Risk control

Risk control is the phase where you mitigate the risks by performing the proposed measures and / or where you accept certain risks.

When you are performing a risk analysis in processes for the first time, it might well be that there are more than a few risks that have to be controlled.

4.6.5 Risk reduction

In this phase you point out which risks are to be mitigated and what corrective and preventive action plan you have thought of to achieve this, including a time line. In Tissue Establishments the factors you can most influence are probability (occurrence) and detectability. The factor of severity of consequences is more difficult, because if consequences happen it mostly affects the quality and safety of the tissue, which means that the consequence is as severe as before. For example, consider the risk that a frozen tissue being distributed by air is delayed, with the result that the tissue is thawed. In this case you cannot influence the severity (loss of tissue) but you can influence the occurrence by taking measures in relation to the amount of dry ice, or the way you transport the tissue, or the detection of the amount of dry ice which was too little to begin with.

4.6.6 Risk acceptance

In this phase you point out which risks are acceptable and why and you also investigate if the risks which are by themselves acceptable do not accumulate to unacceptable risk factors when put together (residual risk).

If you accept a risk, document the decision formally and actively in a report and document the reflections which led to this decision. In Tissue Establishments zero risk is not possible, sometimes we have to accept more risk than would be preferable.

4.6.7 Risk review

By implementing measures to reduce risks, new risks could occur. These risks should not be neglected. In a risk review these risks are considered, as well as the risks which were previously evaluated as not acceptable and which were controlled. If effective measures were taken, the evaluation will show that the risks are mitigated.

A risk evaluation can be frequently planned similar to programming of audits, to make sure in good time that there are no new risk factors which were not analysed. Risk management as part of your quality management system should be integrated and planned like all other quality management activities.

4.6.8 Risk communication

It is important to document the risk management process and outputs in a risk report.

Also it is important not to keep the risk report in a drawer, but to communicate about it with stakeholders other than the employees involved in the risk management process. Implement the measures and communicate the results.Communicate about the risk management process in other quality reports and in management information. Share the results during audits or inspections in the process where a risk assessment has taken place.

4.6.9Risk management tools – Methodology

There are several risk management tools which all include the steps mentioned above. In this chapter we will give a summary of the most commonly used risk management tools in healthcare and which are also mentioned in GMP annex 20. There are also all sorts of ICT applications on the market to help you perform the risk management process, but remember that the pivotal point is always to identify, assess, evaluate and monitor risks.

A simple excel file will help you rate and score risks, but you can also buy a sophisticated application like Bow Tie. The risk management report that is written after the assessment and the measures that are implemented and followed up after implementation, is what makes your risk assessment successful, not the sophisticated tools used.

4.7 Failure Mode Effects and Analysis (FMEA)

Particularly recommended for TE’s is the FMEA methodology, because it is easy to use and moreover, because of the factor of detectability added to severity and occurence. In tissue and cell banking this is often the factor that is easiest to influence to bring about improvements in safety and quality. The severity is generally difficult to influence.

The FMEA method was developed in the aviation industry in the middle of the 1960s. The FMEA model is widely used in the medical and pharmaceutical field. In 2001, the American 'National Center for Patient Safety developed the Healthcare Failure Mode and Effect Analysis (HFMEA).

In 2011 in the Netherlands the national safety management programm of the Ministry of Health has introduced and ' prescribed' the FMEA to all Dutch hospitals as the selected method for prospective risk assessment. The safety management programm has started with the goal to reduce the number of avoidable deaths and diseases of patients in hospitals. An elaborate toolbox is part of the programm for the hospitals.

The FMEA model has been used in an adapted from for medical risk assessments, as has been presented at EATB 2009 by BISLIFE.

4.7.1 Short description of the FMEA method

4.7.1.1 Define occurrence/possibility and severity.

Use a 3 points scale, a five point scale or a ten point scale according to your needs (low, medium, high for example). The scale should ideally be based on quantitative facts or data gathered using spiking experiments or 'sham runs'. For example: how many transport movements in distributions are there and how many non conformities to judge the occurrence.

a) Take the worst case scenario for defining the consequences of the risk factor;
b) Score the occurrence and severity and detectability;
c) Then, add the measures which are already in place in your TE;
d) Now score the occurrence, severity and detectability again;
e) If the risk is not acceptable, state proposals for measures and calculate again;
f) The risk should now be mitigated and be acceptable.

In the subsequent risk management report state which risks are not acceptable or which are acceptable but high, and also state that all risks together form no additional risk.

The FMEA model is explained more in detail in the examples added to this chapter.

4.7.2 Other risk management methods

Hazard Analysis and Critical Control Points (HACCP)

Hazard Operability Analysis (HAZOP)

Fault Tree Anallysis (FTA)

Preliminary Hazard Analysis (PHA)

These Risk management methods are explained in the GMP Annex 20.
For TE processes the FMEA model is recommended, as mentioned above.

4.8 Risk management in relation to legislation and guidelines

4.8.1 EU Directives

The only circumstances where it can be justified that requirements not followed is where a decision is based on risk assessment by the Responsible Person. Otherwise you have to follow all aspects of the EU directives. Sometimes you have to investigate further and therefore you are required to use risk assessments. But this is mainly medical risk assessment, which every doctor performs on a regular basis. The risk management which is being described in this paragraph of the Good Tissue Practices focuses mainly on Quality risk management.

4.8.2 Risk management in relation to GMP/GTP

GMP for pharmaceuticals has now officially been enhanced with annex 20 for Quality Risk Management. It is increasingly acknowledged as important to perform formal documented risk assessments.

Annex 20 lists a description of various models. Annex 20 also lists potential applications for quality risk management.

4.8.3 Training in risk management

Risk management should be incorporated in general TE staff training programmes.

5. TRACEABILITY AND VIGILANCE

5.1.Serious adverse reactions/events

1. Any adverse event occurring during procurement that has or may have resulted in harm to a living donor and the outcome of any investigation to determine the cause must be recorded and reviewed.

2. Member States shall ensure that there is a system in place to report, investigate, register and transmit information about serious adverse events and reactions which may influence the quality and safety of tissues and cells and which may be attributed to the procurement, testing, processing, storage and distribution of tissues and cells, as well as any serious adverse reaction observed during or after clinical application which may be linked to the quality and safety of tissues and cells.

3. All persons or establishments using human tissues and cells regulated by this Directive shall report any relevant information to establishments engaged in the donation, procurement, testing, processing, storage and distribution of human tissues and cells in order to facilitate traceability and ensure quality and safety control.

4. The responsible shall ensure that the competent authority or authorities is or are notified of any serious adverse events and reactions and is or are provided with a report analysing the cause and the ensuing outcome.

5. The procedure for notifying serious adverse events and reactions shall be established by the European Commission.

6. Each TE shall ensure that an accurate, rapid and verifiable procedure is in place which will enable it to recall from distribution any product which may be related to an adverse event or reaction.

7. In cases of disease transmission or infection through the implanted tissues and cells, necessary measures should be taken, including:

1. Immediate notification of severe reactions to the competent authority:
    i. Inherent measures to traceability requirements (information related to implantation centers and recovery centers);
    ii. The recall of the tissues and cells which have already been distributed but not used;
    iii. Stopping the distribution of all tissues and cells involved and recall those remaining in stock (both in the TE or in a third party facilities).
2. Immediate measures for tissue isolation :
    i. Evaluation of predictable actions during the process and implementation of corrective measures and / or preventing actions when appropriate;
    ii. Report of the taken measures to the competent authority

5.2. Notification of serious adverse reactions (Recipients)

1. All adverse events and reactions that are suspected of being related to the quality and safety of tissues or cells should be notified to TEs to allow trends in minor events and reactions to be monitored for continuous improvement purposes.

2. TEs should then apply the adequate tools to assess the severity, the imputability and the impact, in collaboration with appropriate stakeholders, and to identify those serious adverse events and reactions that should be notified to Competent Authorities.

3. Clinical symptoms or situations suggesting that any of the following reactions might have occurred in a tissue or cell recipient (abbreviated descriptions in brackets) should be seen as triggers for an adverse reaction report. Note that the list is not exhaustive.

1. Unexpected primary infections possibly transferred from the donor to recipient (e.g. viral, bacterial, parasitic, fungal, prion) (**Infection - Donor**);
2. Transmitted infection (viral, bacterial, parasitic, fungal, prion) possibly due to contamination or cross-contamination by an infectious agent on the procured tissues, cells or associated materials from procurement to clinical application (**Infection – Tissue/cells**);
3. Hypersensitivity reactions, including allergy, anaphylactoid reactions or anaphylaxis (**Hypersensitivity**);
4. Malignant disease possibly transferred by the tissue/cells (whatever the origin, donor or process) (**Malignancy**);
5. Unexpectedly delayed or absent engraftment, graft failure (including mechanical failure) (**Failure**);
6. Toxic effects from tissues and cells or associated materials (**Toxicity**);
7. Unexpected immunological reactions due to tissue/cell mismatch (**Mismatch**);
8. Aborted procedure involving unnecessary exposure to risk e.g. wrong tissue supplied, discovered after patient is anaesthetised and the surgical procedure has begun (**Undue Risk**);
9. Suspected transmission of genetic disease (**Genetic Abnormality**);
10. Suspected transmission of other (non-infectious) illness (**Other Transmission**).

5.3. Notification of serious adverse reactions (Living donors)

1. Donor adverse reactions with a possible direct effect on the quality and safety of tissue/cells must be reported. These may be immediate, i.e. occurring at the time of the donation or within 8 days of donation, or they may be delayed, i.e. identified after the donation (possibly even many years later).

2. Where allogeneic living donors have been harmed by a donation process but there is no detrimental impact on the quality or safety of the specific tissues or cells concerned; a serious threat to the supply of those tissues or cells could result from the loss of public willingness to donate, or there may be implications for the safety of other living donors. On this basis, it is recommended that Competent Authorities include reporting of such donor adverse reactions in their tissue and cell vigilance programmes and in their annual reports to the EC. If such reactions are the result of an administered drug it will be reportable through the pharmacovigilance system. It should not be reported again through the tissue and cell vigilance system but appropriate communication links between responsible authorities should ensure that the tissue and cell Competent Authority is aware of these reactions.

5.4. Notification of serious adverse events

1. Adverse events (AE) can be detected at any stage in the process from donation to transplantation. Competent authorities will not want to be informed about every deviation from an SOP within a TE. Only serious adverse events should be reported to the competent athority.

2. Seriousness might relate to potential severity of an adverse reaction if the event had not been discovered or to the severity of an adverse reaction that might occur due to a repetition of the event in another place or time.

3. Deviations from Standard Operating Procedures in TEs, or other adverse events, which have implications for the quality and safety of tissues and cells should result in SAE reporting to the Competent Authority when one or more of the following criteria applies:

a) Inappropriate tissues / cells have been distributed for clinical use, even if not used;

b) The event could have implications for other patients or donors because of shared practices, services, supplies or donors;

c) The event resulted in loss of any irreplaceable autologous tissues or cells or any highly matched (i.e. recipient specific) allogeneic tissues or cells;

d) The event resulted in the loss of a significant quantity of unmatched allogeneic tissues or cells.

4. Thus, where the criteria listed above are met, the AE can be considered as posing a serious risk to patient health and in those circumstances it should be reported to the CA. Events that are commonly referred to as 'near misses' are included in the above categories. In the case of assisted reproduction, any type of gamete or embryo misidentification or mix-up is considered to be a serious adverse event and should be notified to the CA.

6. VALIDATION

6.1 Validation

According to Directive 2006/86/EC, validation (or 'qualification' in the case of equipment or environments) means establishing documented evidence that provides a high degree of assurance that a specific process, piece of equipment or environment will consistently produce a product meeting its pre-determined specifications and quality attributes; a process is validated to evaluate the performance of a system with regard to its effectiveness based on intended use"

According to this Directive, the validation is compulsory considering that:

a) All critical[1] equipment and technical devices must be identified and validated(2006/86/ECAnnex 1);
b) The critical processing procedures must be validated and must not render the tissues and cells clinically ineffective or harmful to the recipient' (2006/86/EC Annex 2).

Tissue allograft may have profoundly positive or negative effects on patients. Our products and processes must achieve defined criteria to ensure that they perform as intended. Thus, validation is how we prove (to ourselves and to regulators) that this is the case.

Thus, it is a requirement of the Good Tissue Practices that the TE identify what validation work is needed to prove control of the critical aspects of their particular operations. Significant changes to the facilities, the equipment and the processes, which may affect the quality of the tissues and cells, should be validated. A risk assessment approach should be used to determine the scope and extent of validation

This risk assessment should take into account all the equipment (e.g. autoclave, incubator, freeze drier) facilities (e.g. clean rooms, laminar flow module), electronic systems (e.g. clean rooms environmental monitoring system, tissues processing system) and processes (e.g. musculoskeletal processing, skin processing, clean rooms disinfection, tissue transport, analytical methods) which may impact in the quality of processed tissues.

The results from the risk assessment study regarding the scope of validation activities within a Tissue Establishment should be covered in a Validation Master Plan.

6.1.1Validation Master Plan

The contents of the validation plan shall be at least:

a) Description of the tissue establishment;
b) List of equipment, facilities, electronic systems and processes that need to be qualified or validated;
c) State of validation of each element within the scope;
d) Validation programme;
e) Validation activities responsibilities;
f) Procedures related to validation activities;
g) Criteria for requalification or revalidation.

6.1.2Protocol

The activities of qualification or validation should be described in a protocol containing at least:

a) Objective;
b) Scope;
c) Responsibilities;
d) Related documents;
e) Stages of qualification or validation;
f) Acceptance criteria.

6.1.3Report

A report should be issued reflecting the results of the activities containing at least:

a. Objective;
b) Scope;
c) Responsibilities;
d) Related Documents;

e) Deviations from the protocol;
f) Results;
g) Conclusions.

6.1.4 Equipment qualification

Design qualification (DQ): documented verification that the proposed design of the facilities, equipment, or systems is suitable for the intended purpose.

The first element of the validation of new facilities, systems or equipment could be design qualification.

The compliance of the design with GTP should be demonstrated and documented.

Installation qualification (IQ): documented verification that the equipment or systems, as installed or modified, comply with the approved design, the manufacturer's recommendations and/or user requirements

The protocol should include, but not be limited to the following:

a) verify that all items of– equipment / facility under the requirements in the purchase order ;
b) verify the location and– environmental conditions of the equipment / installation are correct according to the manufacturer's recommendations and internal;
c) verify that these items are installed in accordance with internal specifications and manufacturer correctly identify;
d) verify that the connection of electricity, water, steam, pressure, vacuum, etc., are necessary and that their operating ranges are appropriate for the proper functioning of the installation;
e) verify that the operation of various items of equipment / installation once connected to the mains and put into operation is correct
f) dentify action items that require calibration. Check for appropriate calibration certificates and program and procedure for periodic calibration;
g) check for instructions for use and cleaning of equipment / manufacturer manual and log book of operations of the unit / installation;
h) verify the existence of instructions for performing preventive maintenance.

Operational qualification (OQ): documented verification that the equipment or systems, as installed or modified, perform as intended throughout the anticipated operating ranges

Operational qualification (OQ) should follow Installation qualification. The protocol should include, but not be limited to the following:

a) tests that have been developed from knowledge of processes, systems and equipment;

b) tests to include a condition or a set of conditions encompassing upper and lower operating limits, sometimes referred to as ‘worst case’ conditions;

c) identification of critical operating variables, tests performed, alarms, security devices and acceptance criteria.

The completion of a successful Operational qualification should allow the finalisation of calibration, operating and cleaning procedures, operator training and preventative maintenance requirements. It should permit a formal ‘release’ of the facilities, systems and equipment.

Performance qualification (PQ): documented verification that the equipment and ancillary systems, as connected together, can perform effectively and reproducibly based on the approved process method and specifications.

Performance qualification (PQ) should follow successful completion of Installation qualification and Operational qualification. Although PQ is described as a separate activity, it may in some cases be appropriate to perform it in conjunction with OQ.

The protocol should include, but not be limited to the following:

a) tests, using production materials, qualified substitutes or simulated product, that have been developed from knowledge of the process and the facilities, systems or equipment;
b) tests to include a condition or set of conditions encompassing upper and lower operating limits;
c) process description or reference to protocol development and / or conditioning to validate;
d) list of equipment involved;
e) critical parameters and operating ranges;
f) reference of the procedures involved;
g) description of the tests to be performed, or control variables, sample taking, time and reference method sampling and analytical methods;
h) acceptance criteria.

Qualification of established (in-use) facilities, systems and equipment

Evidence should be available to support and verify the operating parameters and limits for the critical variables of the operating equipment. Additionally, the calibration, cleaning, preventative maintenance, operating procedures and operator training procedures and records should be documented.

6.1.5Clean Rooms and Laminar Flow Hoods Qualification

Following the steps described in the Equipment Qualification paragraph, the tests to be carried out for the Clean Rooms will include at least:

a) Flow and rate of renewals per hour: the speed and rate of renewals per hour according to specified will be checked;
b) Absolute filters Integrity: the grade of sealing of the filters and the absence of leaks in the filter material will be checked;
c) Particle counting: the total count of airborne particles (viable or not) will be checked according to specifications;
d) Temperature / relative humidity: the temperature and relative humidity will be recorded during the test and will be checked according to specifications;
e) Differential pressure: the pressure differential between the different areas will be checked according to specifications;
f) Recovery test (normally tested for A and B classified clean rooms): the time required for a clean room to recover the specified classification after an out of specifications will be checked.

Following the steps described in the Equipment Qualification paragraph, the tests to be carried out for the Laminar Flow Hoods will include at least:

a) Speed and uniformity of the Air: the average speed meets the specified acceptance criteria and that there is uniformity will be checked;
b) Absolute filters Integrity: the grade of sealing of the filters and the absence of leaks in the filter material will be checked;
c) Particle counting: the total count of airborne particles (viable or not) will be checked according to specifications;
d) Electronic test: all the operating controls will be checked (light, UV light, fan) and alarms;

e) Smoke Test (for biological safety cabinets).The test objective is to study the behavior of air inside and outside the cabin with the help of a smoke generator.

All these tests should be performed at least in an ‘at rest’ situation. Additionally, in both cases the particle counting test should be performed also in an ‘in operation’ situation.

6.1.6Process validation

Process validation should normally be completed prior to the distribution of any tissue or cell (prospective validation). In exceptional circumstances, where this is not possible, it may be necessary to validate processes during routine production (concurrent validation). Processes in use for some time should also be validated (retrospective validation).

Facilities, systems and equipment to be used should have been qualified and analytical testing methods should be validated. Staff taking part in the validation work should have been appropriately trained.

Facilities, systems, equipment and processes should be periodically evaluated to verify that they are still operating in a valid manner.

6.1.7Prospective validation

Prospective validation should include, but not be limited to the following:

a) Short description of the process;
b) Summary of the critical processing steps to be investigated;
c) List of the equipment/facilities to be used (including measuring / monitoring / recording equipment) together with its calibration status
d) Finished product specifications for release;
e) List of analytical methods, as appropriate;
f) Proposed in-process controls with acceptance criteria;
g) Additional testing to be carried out, with acceptance criteria and analytical validation, as appropriate;
h) Sampling plan;
i) Methods for recording and evaluating results
j) Functions and responsibilities;
k) Proposed timetable.

Using this defined process (including specified components) a series of batches of the final tissues or cells may be produced under routine conditions. In theory the number of process runs carried out and observations made should be sufficient to allow the normal extent of

variation and trends to be established and to provide sufficient data for evaluation. It is generally considered acceptable that three consecutive batches/runs within the finally agreed parameters would constitute a validation of the process.

Batches, where applicable, made for process validation should be the same size as the routine scale batches.

6.1.8 Concurrent validation

In exceptional circumstances it may be acceptable not to complete a validation program before routine production starts.

The decision to carry out concurrent validation must be justified, documented and approved by authorised personnel.

Documentation requirements for concurrent validation are the same as specified for prospective validation.

6.1.9Retrospective validation

Retrospective validation is only acceptable for well-established processes and will be inappropriate where there have been recent changes in the composition of the tissues or cells, operating procedures or equipment.

Validation of such processes should be based on historical data. The steps involved require the preparation of a specific protocol and the reporting of the results of the data review, leading to a conclusion and a recommendation.

The source of data for this validation should include, but not be limited to batch processing and packaging records, process control charts, maintenance log books, records of personnel changes, process capability studies, finished product data, including trend cards and storage stability results.

Batches selected for retrospective validation should be representative of all batches made during the review period, including any batches that failed to meet specifications, and should be sufficient in number to demonstrate process consistency. Additional testing of retained samples may be needed to obtain the necessary amount or type of data to retrospectively validate the process.

For retrospective validation, generally data from ten to thirty consecutive batches should be examined to assess process consistency, but fewer batches may be examined if justified.

6.1.10Cleaning and Disinfection Validation

Cleaning and disinfection validation should be performed in order to confirm the effectiveness of a cleaning or disinfection procedure. The rationale for selecting limits of carry over of product residues, cleaning agents and microbial contamination should be logically based on the materials involved. The limits should be achievable and verifiable.

Validated analytical methods having sensitivity to detect residues or contaminants should be used. The detection limit for each analytical method should be sufficiently sensitive to detect the established acceptable level of the residue or contaminant.

Normally only cleaning or disinfection procedures for product contact surfaces of the equipment need to be validated. Consideration should be given to noncontact parts. The intervals between use and cleaning or disinfection as well as cleaning or disinfection and reuse should be validated. Cleaning or disinfection intervals and methods should be determined.

For cleaning and disinfection procedures for products and processes which are similar, it is considered acceptable to select a representative range of similar products and processes. A single validation study utilising a ‘worst case’ approach can be carried out which takes account of the critical issues.

Typically three consecutive applications of the cleaning or disinfection procedure should be performed and shown to be successful in order to prove that the method is validated.

‘Test until clean’. is not considered an appropriate alternative to cleaning validation.

Products which simulate the physicochemical properties of the substances to be removed may exceptionally be used instead of the substances themselves, where such substances are either toxic or hazardous.

6.1.11Validation of Analytical Methods

Analytical methods should be validated to include consideration of characteristics included within the ICH guidelines on validation of analytical methods (ICH Q2 (R1)). The degree of analytical validation performed should reflect the purpose of the analysis.

Appropriate qualification of analytical equipment should be considered before starting validation of analytical methods.

Complete records should be maintained of any modification of a validated analytical method. Such records should include the reason for the modification and appropriate data to verify that the modification produces results that are as accurate and reliable as the established method.

6.1.12Revalidation

The revalidation will be needed when there is a change in any equipment, facilities or process, considered significant because it affects the quality of the product / process or have implications for the GMP or the RD 1301/2006. These changes should be approved through a change control procedure. Otherwise, when the product quality review confirms that the system or process is consistently producing material meeting its specifications, there is no need for revalidation.

6.2 Example of Transport validation

6.2.1 Objective

The objective of this study is to ensure that the packaging system used by the TE for each tissue types shipment, is able to maintain adequately the physical-chemical conditions of the product during transportation.

6.2.2 Scope

- Porexpan box 17L (-80ºC)
- Porexpan box 17L (4ºC)
- Porexpan box 32L (-80ºC)
- Porexpan box 2L (4ºC)

6.2.3 Responsibilities

To be defined internally

6.2.4 Related documents

LOG-PNT-004: Shipments procedure

6.2.5 Critical validation elements

a) Which and how many tissues?
b) Which container?
c) Which refrigerant and how much?

d) How long?
e) Environmental temperature?

Shipment	Tissue	How many	Packaging	Cooler	Quantity	Time	External Tª
17L (-80ºC)	MSK grafts	3 tendons	17L	Dry ice	5kg	72h	35ºC
17L (-80ºC)	MSK grafts	3 tendons	17L	Dry ice	5kg	72h	25ºC
17L (+4ºC)	Skin grafts	3 glycerol bags	17L	Cooler	6 units	48h	35ºC
17L (+4ºC)	Skin grafts	3 glycerol bags	17L	Cooler	5 units	48h	25ºC
32L (-80ºC)	MSK grafts	1 long graft	32L	Dry ice	8kg	72h	35ºC
32L (-80ºC)	MSK grafts	1 long graft	32L	Dry ice	8 kg	72h	25ºC
2L (+4ºC)	Cells syringe	1 syringe	2L	Cooler	2 units	48h	35ºC
2L (+4ºC)	Cells syringe	1 syringe	2L	Cooler	2 units	48h	25ºC

6.2.6 Method to perform the study

a) Is it going to be a real or simulated (using an incubator) process?
b) How many points are being monitored?
c) How is the tissue packaged?

a) The tissue is packaged as per instructions showed in LOG-PNT-004 document.
b) The temperature probe is located fixed to the tissue and all the components packaged in the final shipping box.
c) During the following 72h the box will stay in the incubator at 25ºC.
d) At the end of this period the probe temperature values are downloaded and the graphics are analysed.
e) All the previous steps are repeated changing the temperature in paragraph c) to 35ºC.
f) All the tests will be performed in duplicate

6.2.7 Results and acceptance criteria

a) Time and temperature;
b) Tissue integrity;
c) Transport container integrity.

	Acceptance criteria				Results		
Shipment	**External Tª**	**Tissue integrity**	**Packaging integrity**	**Tª range and time**	**Tissue integrity**	**Packaging integrity**	**Tª range and time**
17L (-80ºC)	35ºC	OK	OK	48h between -60ºC and -80ºC	OK	OK	
17L (-80ºC)	25ºC	OK	OK		OK	OK	
17L (+4ºC)	35ºC	OK	OK	24h between +1ºC and +8ºC	OK	OK	
17L (+4ºC)	25ºC	OK	OK		OK	OK	
32L (-80ºC)	35ºC	OK	OK	48h between -60ºC and -80ºC	OK	OK	
32L (-80ºC)	25ºC	OK	OK		OK	OK	
2L (+4ºC)	35ºC	OK	OK	24h between +1ºC and +8ºC	OK	OK	
2L (+4ºC)	25ºC	OK	OK		OK	OK	

6.2.8 Conclusions

To be defined internally

6.3: Facilities disinfection

6.3.1. Objective

Validation of the processing classified area through the evaluation of the feasibility and efficiency of the disinfection products and procedures.

6.3.2. Scope

The scope of the validation study covers the disinfection of the clean rooms classified grade B.

6.3.3. Responsibilities

To be defined internally

6.3.4. Related documents

- PR-SMT-012: clean rooms disinfection

6.3.5. Critical validation elements

a) Classification and activity in the clean rooms;
b) Disinfection products;
c) Disinfection procedure;
d) Monitoring plan (may need to be more extent than the routine plan).

6.3.6. Method to perform the study

a) Determine the worst case situation (if possible). As long as you can determine the most contaminating process and link it to an individual clean room, the validation study will be able to be conducted only in that clean room and consider it as a representative case.
b) The disinfection procedure will be applied three consecutive times immediately after three processing activities. This means that the disinfection procedure will always have to be applied immediately after the processing activities in routine.
c) The alternation of the disinfection products is strongly recommended so the disinfection procedure must be applied using all the products involved in the disinfection program. Consequently at least six runs will be needed.
d) The period of time while the disinfection efficiency is kept must be determined through microbial monitoring.

6.3.7. Results and acceptance criteria

CLEAN ROOM (GRADE B)		PERFORMED/DATE	ACCEPTANCE CRITERIA	RESULT	C/NC
1.B1	Bacteria monitoring point		5 ufc/plate		
1.B2	Bacteria monitoring point		5 ufc/plate		
1.B3	Bacteria monitoring point		5 ufc/plate		
1.B4	Bacteria monitoring point		5 ufc/plate		
1.B5	Bacteria monitoring point		5 ufc/plate		
1.B6	Bacteria monitoring point		5 ufc/plate		
1.H1	Fungi monitoring point		5 ufc/plate		
1.H2	Fungi monitoring point		5 ufc/plate		
1.H3	Fungi monitoring point		5 ufc/plate		
1.H4	Fungi monitoring point		5 ufc/plate		
1.H5	Fungi monitoring point		5 ufc/plate		
1.H6	Fungi monitoring point		5 ufc/plate		
1.A1	Air monitoring point		10 ufc/m3		
1.A2	Air monitoring point		10 ufc/m3		

Repeat this monitoring plan for each process.

7. CRITICAL THIRD PARTY AGREEMENTS

1. TEs shall establish written agreements with a third party each time an external activity takes place which influences the quality and safety of tissues and cells processed in co-operation with a third party, and in particular in the following circumstances:

a) Where a TE entrusts one of the stages of tissue or cell processing, control, packaging, storing or distribution to a third party;

b) Where a third party provides goods and services that affect tissue or cell quality and safety assurance, including their distribution;

c) Where a TE provides services to a TE which is not accredited;

d) Where a TE distributes tissue or cells processed by third parties.[2]'

2. The written agreements should include at least:

a) A clear description of the scope of the agreement;

b) Names, roles and signatures of those taking responsibility for each party;

c) Detailed description of the responsibilities of each party in relation to safety and quality of tissues, including any quality system requirements considered necessary;

d) Provision for auditing of the third party by tissue establishment staff on a routine and/or exceptional basis;

e) Requirements for data protection where third parties have access to any information of a personal nature (donor or recipient);

f) Requirements for maintenance of traceability for tissues and any materials that come into contact with them;

g) Requirements for archiving of traceability and quality system records;

h) Any requirements for certification/licensing of the third party that might be appropriate (e.g. in the case of a serology testing laboratory);

i) Duration of the agreement and the timing of reviews;

j) Details of when and how adverse incidents (reactions or events) should be communicated between the TE and the third party and how they should be investigated;

k) The way in which the Responsible Person releasing the tissue/cell batch for application ensures that any critical step performed by a third party was carried out in compliance with the requirements laid down;

l) Where tissue processing is carried out by a third party, the agreement should specify who is responsible for purchasing materials, testing and releasing materials, undertaking processing and quality controls, including in-process controls, and who has responsibility for sampling and analysis;

m) Where relevant, processing, analytical and distribution records, and reference samples should be kept by, or be available to, the tissue establishment. Any records relevant to assessing the quality of tissue/cells in the event of complaints or a suspected defect must be accessible and specified in the defect/recall procedures of the Contract Giver;

n) The contract should permit the competent authorities to inspect the third party if they wish to do so;

[2] Directive 2004/23/ec of the European Parliament and of the Council (Art 24)

o) The way in which data and samples affecting the traceability, quality or safety of tissues and cells, are provided to the tissue establishment in case of resolution of the agreement.

3. TEs shall evaluate and select third parties on the basis of their ability to meet the standards laid down in in 2004/23/EC.

4. TEs shall keep a complete list of the agreements that they have established with third parties.

5. Agreements between TEs and third parties shall specify the responsibilities of the third parties and detailed procedures.

6. TEs shall provide copies of agreements with third parties at the request of the competent authority or authorities.[3]

8. IMPORT AND EXPORT

Preamble

Although the number of transplantations each year has grown rapidly over the past two decades, the demand for transplantation using human cells, tissues and organs has increased significantly, resulting in a continuing shortage of human material, particularly organs. Few countries are near to being self-sufficient in the provision of cells, tissues and organs for transplantation.

Efforts should be made to increase the donation of human material, to achieve national self-sufficiency, and to prevent 'transplant tourism' and the 'trafficking' of human cells, tissues and organs.

Success in increasing donations of cells, tissues and organs in order to meet global needs depends on public acceptance of safe, legal donation and transplantation, together with public awareness of the dangers of commercial trade and 'trafficking'.

With the growing global circulation of transplantable material, traceability is a major concern for transplant professionals and surveillance systems. There would be significant advantages in developing a common basis for a global system for coding transplantable material, especially cells and tissues. The use of a global coding system could also offer benefits in combating commercial trade.

The allocation of organs, cells and tissues should be guided by clinical criteria and ethical norms, not financial or other considerations. Allocation rules, defined by appropriately constituted committees, should be equitable, externally justified, and transparent[4]

[3] Directive 2004/23/ec of the European Parliament and of the Council (Art 24)

[4] Human organ and tissue transplantation. Report by the Secretariat. SIXTY-SECOND WORLD HEALTH ASSEMBLY. March 26, 2009.

1. The EUTCD (transposed into EU Member State laws, regulations and standards) should ensure that, within the EU, human tissues and cells, whatever their intended use, are of comparable safety and quality even if procured in another Member State, particularly in order to prevent the transmission of diseases and therefore to protect the health of EU citizens who receive human tissue cells and treatments.

2. In addition, wherever tissues and cells for human application enter or leave the EU, they should have met the standards or equivalent to those laid down in the EU Member State laws, regulations and standards, which may be more stringent than the EUTCD.

3. The terms ‘import’ and ‘export’ relate to the exchange of goods (human tissues in this case) respectively from or to countries outside of the EU.

4. The transit of tissues (the import of tissues only for transfer to another EU Member State or for export to a non-EU country) should be considered as an import followed, possibly after a processing and/or storage step, by a transfer or an export.

5. A fair balance in the exchange of human tissue must be sought in order not to undermine the legitimate public health interests in the importing and exporting countries.

6. The import and export of tissues should not be guided by financial considerations (profit-maximizing practices).

7. TEs wishing to import or export tissues should be able to demonstrate that the purposes for which they wish to import or export such material cannot be adequately met by comparable material available from sources within those countries, or is for a particular purpose which justifies import or export. TEs should be able to document the need for importing or exporting in terms of accessibility, quality, timeliness of supply, risk of infection, or quality of service. Such documentation should be available for inspection by the CA.

8. Imports and exports of tissues may only be undertaken by TEs accredited, designated, authorised or licensed for the purpose of those activities.

9. The transport conditions should maintain the quality and safety of the tissues.

10. TEs that import and export tissues shall ensure that they comply with the requirements of:

    a. The relevant national laws, regulations and standards of the importing and exporting countries.

    b. The WHO Guiding Principles on Human Cell, Tissue and Organ Transplantation (provide an orderly, ethical and acceptable framework for the acquisition and transplantation of human cells, tissues and organs for therapeutic purposes).

    c. The Declaration of Helsinki (reinforces consent and ethics issues).

11. The importing or exporting TE should have in place procedures for verifying the compliance of the tissues to the above-mentioned requirements. It is recommended for TEs to perform audits of the TEs from and to which they regularly import or export considerable amounts of tissues. Such an audit should include a review of compliance with the above-mentioned requirements.

12. Approval of imported tissues and approval for exportation of tissues are done under the responsibility of the Responsible Person of the importing or exporting TE.

13. The terms of import and export of tissues must be described in a document detailing the responsibilities and commitments of each party.

14. Important points of concern:

    Source

    a. Importing TEs should satisfy themselves, with due assurance from their collaborators abroad, that any material intended for import is sourced consistently with the legal and ethical requirements in both the importing and exporting countries.

    b. If the importing TE cannot ensure that ethical standards have been put in place, the tissues should not be imported.

    Consent

    a. Importing TEs should satisfy themselves that, in the countries from which they seek to import tissue, the gaining of consent for the purpose to which the tissue is

subsequently put is part of the process by which the material is obtained (including providing donors, their legal representatives or their family with the information that their tissues may be exported for use abroad).

b. The importing TE should have in place reliable procedures which clearly set out the evidence indicating how informed consent was obtained, including safeguarding the confidentiality of all information relating to consent.

Import/export register

a. Relevant data concerning the import and export of tissues should be retained in a safe place in the TE and should be available for inspection by the CA. This import/export register should include details of the reason why the decision was made to import or export the tissues, of when the tissues were imported or exported and where from or to, the uses to which they were put, when the tissues were transferred elsewhere and to whom.

Traceability

a. Imported tissues must be traceable from the donor to the recipient and vice versa. This traceability shall also apply to all relevant data relating to products and materials coming into contact with these tissues.

b. A unique code must be assigned to each donation and to each of the products associated with it.

c. All imported and exported tissues must be uniquely identified with a label that contains the information or references allowing a link to the information regarding tissue procurement, reception, processing, storage and distribution or disposal. The label shall at all times mention the name and address of the facility where the tissue was procured and the TE that performed the procurement.

d. TEs shall keep the data necessary to ensure traceability at all stages. Data required for full traceability (see ANNEX VI of COMMISSION DIRECTIVE 2006/86/EC of 24 October 2006), including the import/export register,shall be kept for a minimum of 30 years after clinical use or the expiry date, in an appropriate and readable storage medium acceptable to the CA. Data storage may also be in electronic form.

9. CONTINUITY PLANS

1. TEs shall have in place a continuity plan (with adopted procedures and concluded agreements) to ensure that, in the event of termination of their banking/servicing activities (partly, temporarily or permanently) for whatever reason, the tissues in their management shall be transferred to other TEs.

2. This continuity plan should not undermine legitimate public health interests and should not be guided by financial considerations (profit-maximizing practices).

3. When the continuity plan implies that tissue could be exported (transferred to a country outside the EU), the export should comply with the requirements in section B.4.3.3. Import and export.

4. The accepting TEs need to be accredited, designated, authorized or licensed for the purpose of the activities they will need to assume when accepting the tissue.

5. The accepting TEs need to be able to handle the anticipated amounts of transferred tissue (e.g. sufficient stocking capacity).

6. The transferred tissue needs to be accompanied by its relevant documentation (including traceability data) and material concerning the quality and safety of the tissue (including retain samples).

7. The transport conditions should maintain the quality and safety of the tissues.

8. The transfer of tissues, documentation and material are done under the responsibility of the Responsible Persons of the ceasing and the accepting TEs.

9. The accepting TEs should have in place procedures for verifying the compliance of the tissues to the ethical and legal requirements.

10. The terms and conditions of the transfer of tissues shall be described in an agreement (service level agreement or convention) detailing at least:

    a. The responsibilities and commitments of each party.

b. The type and anticipated quantities of tissues that will be transferred.

c. The type and anticipated quantities of documentation that will be transferred.

d. The type and amount anticipated quantities of material (e.g. retain samples) that will be transferred.

e. The transport conditions for tissue, documentation and material.

11. It is however possible that a meaningful transfer of tissues can not be agreed upon (or is impossible). In this case the CA shall determine the fate of the tissues.

10. TISSUE ESTABLISHMENT DOSSIER

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