

**Guidelines from the German Society of Surgery
(Deutsche Gesellschaft für Chirurgie)
on Good Professional Practice (GPP)
for the Procurement of Human Tissue and Cells
for Drug Production**



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1. Foreword

These Guidelines established by the German Society of Surgery (Deutsche Gesellschaft für Chirurgie, DGCH) on Good Professional Practice (GPP) describe the requirements for procurement organisations – i.e., institutions involved in the procurement of human tissues and cells in accordance with § 1a no. 4 of the German Transplantation Act (TPG) (§ 20b paragraph (para.) 1, sentence 2 AMG (German Medicines Act) [1]) – and define the necessary prerequisites and measures for quality assurance (QA), and for the complete traceability of all procured tissues.

The Guidelines also take into account the different potential risks, to donors and recipients, relative to the latest advancements in medical science and technology in the procurement of tissues and cells. The Guidelines address the special structural, spatial, personnel, organizational and technical prerequisites and describe the general and special conditions for autologous and allogeneic tissue donation, as well as procurement of tissue from living and deceased donors, taking into account the relevant provisions in German and European legislation (notably the Tissue Directive 2004/23/EC of the European Parliament and the Council dated 31 March 2004 dealing with the determination of quality and safety standards for the donation, procurement, testing, preservation, storage and distribution of human tissues and cells [2] and its Enforcement Directive 2006/17/EC dated 8 February 2006, which addresses the technical requirements for the donation, procurement and testing of cells and tissues [3]).

The term “state-of-the-art medical science and technology” is used repeatedly to highlight that the Guidelines first and foremost apply to the practice of medicine and specify responsible, current standards. As regards the procurement of tissues and cells, the principal regulation is the Tissue Act (§ 16b TPG), which states that standards and guidelines are normally defined by the German Federal Medical Council. Such guidelines and standards of practice are produced in collaboration with experts in the relevant medical disciplines and related societies [4]. The recommendations of professional medical associations, such as DGCH’s current GPP-Guidelines, are one component of the Medical Council standards.



The German Federal Medical Council regulations specify the requirements, based on state-of-the-art medical science and technology, for the procurement and analysis of tissue (and cells) by tissue procurement institutions in accordance with § 8d TPG. Compliance with these regulations is obligatory when seeking to obtain a permit relating to § 20b para. 1 sentence 3 no. 4 AMG (German Medicines Act). These are one of the supplements to the currently pending German Federal Ministry for Health and Social Security ordinance in accordance with § 16a TPG [5].

The GPP-Guidelines are intended to assist tissue procurement organisations in the establishment of a quality assurance system and to facilitate the work of the relevant authorities in evaluating applications for procurement permits, including the inspection of procurement facilities. The Guidelines do not deal with specific occupational safety measures for staff and other personnel in a procurement organisation, nor do they touch on the relevant legal provisions and directives for this particular area.

The GPP-Guidelines are divided into chapters covering the different aspects of quality assurance of tissue procurement for donors and/or recipients. Each chapter discusses the principles and the relevant quality assurance objective, and describes the measures by which this objective can be achieved. The explanations provided are intended to capture the main aspects of quality assurance. In addition, definitions of important and common technical terms – as provided by the legislator – have been included in the glossary (chapter 18).

Besides the methods described in these Guidelines, there are certainly other methods that enable compliance with the principles of quality assurance. These Guidelines are not intended to restrict or obstruct development of new, validated quality assurance concepts or methods, provided these can be demonstrated to be at least equivalent to the methods described below.

The present Good Professional Practice Guidelines (GPP-Guidelines) will be reviewed at regular intervals and revised as necessary to reflect advancements in science and technology.



2. Scope

The scope of the GPP-Guidelines is limited to the territory of the Federal Republic of Germany. Contrary to the EC-GMP Guideline, which applies across the entire territory of the European Union (EU) for the uniform interpretation of the principles and guidelines for Good Manufacturing Practice (GMP) [6], the present GPP-Guidelines have not been adopted by the European Union [7].

These GPP-Guidelines are applicable to tissue procurement organisations according to § 20b para. 1 sentence 1 of the AMG. These are facilities according to § 1a no. 8 TPG (such as hospitals, clinics, medical practitioners, tissue banks) where human tissue (and cells) are harvested, stored and distributed for human application and drug manufacture in accordance with § 1a no. 4 TPG (also in the form of trial medication according to § 3 para. 3 of the GCP ordinance [8]). The Guidelines should, however, also be taken into account whether exceptions in § 4a sentence 1 no. 3 or no. 4 AMG rule out the application of the AMG.

Any other production of drugs using harvested tissue that goes beyond the procurement as specified in § 20b para. 1 sentence 1 and 2 AMG, as well as the clinical application of these drugs, are not part of these GPP-Guidelines.

The Guidelines do also not apply to the use of human tissue and cells for research purposes, such as *in-vitro* experiments, animal studies, and other uses that do not involve application in or on the human body. The Guidelines also do not apply to the procurement and manufacture of blood products or blood components according to § 2 no. 3 of the Transfusion Act (TFG), which fall under Good Manufacturing Practice (GMP) regulations.

The definitions of the GMP-regulations (Good Manufacturing Practice) do not apply to the procurement of human tissue and cells used for the production of drugs if the procurement takes place according to the rules and regulations of Good Professional Practice.



3. Quality Assurance and Definition of Responsibilities

3.1. Responsible Medical Personnel in the Procurement Organisation

According to § 8d para. 1 TPG and notwithstanding the provisions of the German Medicines Act (AMG), a facility which harvests or analyses tissue may only operate if a doctor is in attendance (referred to as "medical personnel" (German: ärztliche Person) in § 20b para. 1 sentence 3 no. 1 AMG), who has the necessary expertise according to state-of-the-art medical science.

According to article 17 paragraph 2 a) of the EC Tissue Directive 2004/23/EC, every tissue establishment shall designate a supervisor, i.e. a qualified medical officer, who is responsible for compliance with the relevant, valid laws, ordinances, regulations, guidelines and recommendations regarding procurement procedures. This person (hereinafter referred to as "responsible medical person") is responsible for the formulation and implementation of a quality assurance system (QA system) and for the implementation, management, maintenance and compliance with valid quality and safety measures, provided the procurement organisation is not in a contractual relationship with a manufacturer that has a manufacturing license in accordance with § 13 AMG, or with a processing company that has a license in accordance with § 20c AMG, whose QA system it must adopt.

The position of the responsible medical person with "medical" responsibility for the procurement organisation must be occupied by a qualified medical doctor (refers to both male and female doctors in the GPP-Guidelines) who has the required expertise in tissue procurement. This will normally be a medical professional with a great deal of experience.

The responsible medical person is responsible for workflow management and communication in the procurement organisation and defines staff duties and responsibilities, as well as the approval procedures for harvested tissue and cells, to ensure the necessary compliance with the quality and safety standards for procurement, testing, storage and distribution to manufacturers (§ 13 AMG) or processing companies (§ 20c AMG) throughout the entire work process.



This person must ensure that doctors or other qualified persons authorised to harvest tissues and cells, and their assistants, are adequately trained and qualified to perform all their tasks in an expert, safe and reliable manner. The responsible person must also ensure that the professional knowledge of the staff remains current with advancements in medical science and is regularly updated through training. The responsible medical person shall keep a list of trained and authorized doctors or persons, including the individual's date of authorisation and signature.

Tissue procurement can also be performed in a healthcare establishment or a unit of a hospital or another body with only one medical doctor in attendance, provided that the legal provisions and the specifications of the GPP-Guidelines are met. In this case, the medical doctor performing the procurement is also the responsible medical person.

3.2. Brief Description of the QA System for Procurement Organisations

Quality assurance (QA) is the duty of the management of the respective procurement organisation, i.e. the responsible medical person, who defines the competencies and responsibilities, the content of the quality assurance document, and puts in place appropriate implementation and inspection mechanisms. The QA system must conform to the type and scope of the tissue or cell procurement undertaken, to ensure the highest possible standard of safety and benefit for donor and recipient.

The QA system must be integrated into the existing quality management system (QM system) of the tissue establishment and must provide for the active involvement of the management of the procurement organisation and personnel in all the areas concerned. These conditions must be created by the responsible body of the tissue harvesting facility.

QA covers all personnel, organisational, technical and normative activities that are needed to guarantee, improve and further develop the quality and safety of patient care as further advancements in medical sciences are made (see especially §§ 135a, 136 and 137 SGB V).



Achievement of quality objectives consistent with the standards set by these regulations, and continual, ongoing compliance, must be guaranteed through appropriate control mechanisms, and evaluated with regular inspections based on defined quality criteria.

It is recommended that QA be defined in the form of standard operating procedures (SOPs) in a quality manual, which describes the individual, clearly defined work processes. The written instructions must include all applicable methods and procedures and must be accessible to all persons and authorised bodies concerned.

According to national legal regulations, QA of the tissue procurement organisation must comply in particular with the following requirements:

- name, job description and qualification of the director and his/her deputy,
- criteria and analysis methods for the determination of donor suitability,
- information for donors or their relatives,
- requirements for rooms and methods of tissue procurement,
- requirements for surgical instruments used in tissue procurement,
- requirements for specialist medical and assisting personnel,
- training and qualification of specialist medical and assisting personnel,
- hygiene measures (hygiene plan with all technical, operational and organizational activities),
- encoding, i.e. identification, traceability and prevention of mix-up of harvested tissue (also of blood samples for diagnostic purposes, if applicable),
- approval procedures,
- packaging, storage, distribution and transportation of the harvested tissue,
- corrective actions for the occurrence or suspected occurrence of serious incidences or serious adverse reactions,
- duty to report,
- documentation.

All instructions must be reviewed at regular intervals and must be approved by the person(s) in charge before taking effect. In the event of process change, no longer valid instructions must be withdrawn and destroyed. The original document must be stamped as invalid and archived.



It is recommended that a document control process be established to maintain a history of document reviews and changes. This ensures that only the most current version of each document is in use. An effective QA system also includes reviewable and complete documentation for the creation, change and replacement of SOPs.

3.3. Definition of Responsibilities

Manufacturers with a manufacturing licence in accordance with § 13 AMG or processing companies with a licence in accordance with § 20c AMG can adopt parts of the QA regulations, e.g. in form of SOPs for tissue procurement. The procurement organisation can also be integrated into the QA system of the manufacturer or the processing company for which it harvests tissue under contract. No matter how this is regulated, it is important that the responsibilities and duties in the various sub-sections are always clearly defined and established in writing.

If the procurement organisation and the manufacturer or processing company are not represented by the same person (or are not the same legal entity), the respective responsibilities and duties must be specified in written agreements.

Agreements between the procurement organisation and manufacturers or processing companies and other third parties must conform to § 9 of the German Ordinance for the Production of Medicinal Products and Active Substances (AMWHV) and must adhere to the regulations of Article 24 of the Directive 2004/23/EC. According to these legal provisions, the responsibilities and methods must be stipulated in detail in the agreement. This applies especially to donor selection criteria, procurement method and donor documentation.

The procurement organisation can also conclude contracts with third parties that are only contracted for transportation and analysis, not for manufacture. Here also the contracts must conform to § 9 AMWHV and be designed such that responsibilities/liabilities are clearly defined and separated between the client and the contractor.

The procurement organisation must also ensure that the testing laboratory it has commissioned is capable of handling the relevant tasks. This capacity is certified to the testing laboratory through a permit according to § 20b para. 1 AMG.



Alternatively, it is possible to ensure the qualification of the testing laboratory through a contract with the manufacturer or the processing company with licenses as specified in § 13 or § 20c AMG (§ 20b para. 2 AMG). The client must audit the contractor. Companies commissioned by a procurement organisation must be named in the QA system of the procurement organisation.

4. Documentation

4.1. General Requirements

The entire process, from donor selection through procurement and processing of tissue and cells, to the therapeutic application in the recipient, must be completely documented (see Article 8 of the Tissue Directive 2004/23/EC). The procurement organisation is responsible for documenting all processes and procedures within its scope of action and responsibility. In this context, particular attention must be paid to observing the provisions specified in §§ 14 and 15 TPG.

The documentation of each individual process step is the responsibility of the authorised medical doctor in charge. The records must be kept diligently, must be complete, and must remain confidential and inaccessible to unauthorized persons. The confidentiality regulations of Article 14 of the Directive 2004/23/EC and the German data protection laws must be observed.

All process steps, activities, and especially clearance of the tissue for therapeutic application or for dispatching to the manufacturer or the processing company, must be recorded, complete with the date and signature of the medical doctor in charge of the tissue procurement. The data entries must be legible and be written with permanent ink.

Corrections or retrospective amendments in the documentation may only be carried out by authorized persons and must be dated and signed by the person making the corrections or amendments. The original entries may not be deleted or obliterated, but must remain legible.

The procurement organisation must retain all records and documents associated with the tissue procurement for a period of 30 years after expiry of the tissue expiry date, unless the § 15 TPG stipulates a shorter document retention period. The data must be deleted or anonymised after 30 years.



4.2. Special Requirements

The documentation system must allow access to all relevant data relating to the tissue procurement at any time and must ensure the completeness of the data and the protection of data. Data can be recorded and archived either on paper or electronically (see Article 8 paragraph 4 Directive 2004/23/EC). Electronic data recording and archiving requires the use of a validated process to prevent the loss of data. The documentation archive may have to be approved by the respective authority (see Appendix IV, no. 1.4.4. of the Directive 2006/17/EC).

Regardless of the form of data recording and archiving, it must as a matter of principle ensure that the data kept for tracking purposes are flawless, i.e. that they are preserved and remain legible for the legally prescribed archiving period of 30 years.

The complete donor documentation must be stored within the premises of the procurement organisation in accordance with § 8d para. 2 TPG and additionally, or at least, in the form of a procurement report (see also chapter 11 of the GPP-Guidelines) by the manufacturer or the processing company. The data must be archived in compliance with data protection requirements according to § 14 TPG in a special area in rooms which are registered and approved according to § 20b AMG.

If a procurement organisation, where the documentation is stored, ceases operations, appropriate steps must be taken to ensure that the documentation remains intact and available throughout the legally prescribed retention period.

5. Layout and Equipment of Procurement Organisations

5.1. Preliminary Remarks

The main objective of all measures taken in regard to the spatial, technical and hygienic requirements for procurement organisations is the protection of the donor, recipient, and personnel, against infection and other adverse events. This protection is ensured with operational-organisational, functional-structural and instrument-technical preventive measures [9,10].



The mutual weighting of these measures for a tissue or cell donation is mainly determined by the extent, (i.e. invasiveness) of the procedure, the degree of contamination of the body part from which the tissue or cells are taken, and by the on-site conditions at the tissue establishment.

Requirements vary depending on whether the donor is living or non-living. The requirements for the above mentioned preventive measures differ for the procurement of different tissues or cells and depend on the specific circumstances of the donation.

Principally, however, and regardless of the invasiveness of the procedure, the degree of contamination of the harvesting region and other relevant factors, hygienic work conditions, taking into consideration the necessary medical instruments and manpower, must be ensured both with living and non-living donors.

In this context, the recommendations of the Commission for Hospital Hygiene and Infection Prevention at the Robert Koch Institute (RKI) set forth in 2000, dealing with the hygiene requirements during surgery and other invasive procedures [11], serve as general specifications and must be observed. These GPP-Guidelines do not impose any additional requirements related to hygiene and the spatial layout and equipment of tissue establishments, beyond those of the RKI. These Guidelines only take into account already existing safety regulations and preventive measures set out by the RKI for surgery and other invasive procedures, which also apply for the surgical procurement of human tissues and cells and the respective instruments and equipment used.

If the manufacturer or the processing company to which the procured tissue is supplied for reprocessing imposes additional reasonable conditions or special requirements for the room layout, or the technical and sanitary equipment of a tissue harvesting facility, the procurement organisation must also comply with these specifications.



5.2. Designation and Determination of Rooms for Tissue Procurement

The rooms (operating, minor procedure, treatment, autopsy or other designated rooms) in which tissue is procured must be designated and clearly assigned in a layout plan. The layout plan must be submitted to the Drug Control Authorities on request.

The rooms in which tissue is harvested need not necessarily be designated if the procedure is performed on non-living donors. If tissue procurement from non-living donors is not performed in the registered and licensed rooms, this must be noted in the procurement records (see Appendix IV, no. 1.3.4 of the Directive 2006/17/EC). The medical doctor in charge of the procurement must assess and document the suitability of the room in which the tissue procurement takes place.

Rooms for tissue harvesting are considered suitable principally if the tissue is withdrawn and prepared in rooms that are appropriately equipped for this special procedure, and if the standard requirements are complied with, and the necessary hygiene measures are in place. The regulatory standards for this are defined by the RKI in "Hygiene requirements during surgery and other invasive procedures" [11].

The degree of contamination of the body region concerned plays a role in the selection of rooms used for tissue procurement; these regions are classified either as not contaminated (aseptic, i. e. physiologically germ-free), potentially contaminated (conditional aseptic) or contaminated (physiologically parasitised). Whether tissue procurement is performed on a living or non-living donor is relevant here.

Tissue procurement may not be performed on infected regions (though infected regions are distinguished from physiologically parasitised regions), or in the presence of a systemic infection. Exemptions to this regulation must be observed for eye cornea donors with bacterial sepsis (see Appendix I, no. 1.1.5. of the Directive 2006/17/EC).



5.3. Equipment and Furnishings

The operating rooms, their equipment and furnishings must be easy to clean and disinfect. Tissue procurement must be performed in aseptic rooms. The principal objective, prevention of cross-contamination, can be achieved by using disposable instruments.

Surgical instruments used for tissue procurement must be of very high quality, and must be qualified according to Article 2 paragraph 7 of the Directive 2006/17/EC, or else specially certified.

If, for practical reasons, reusable instruments or instrument sets are used, they must be cleaned and sterilised to remove infectious agents or other contaminants. The reprocessing/sterilization procedure must be validated and documented, in conformance with standards (see Appendix IV, no. 1.3.9. of the Directive 2006/17/EC).

Reusable instrument sets for tissue procurement must be regularly inspected and serviced (see also chapter 5.5. of the GPP-Guidelines). Instruments and tools which come into direct contact with the tissue during the procurement procedure must be included in a device or equipment list. CE-certified and CE-labelled medical devices and instruments should be used whenever possible. The medical personnel must be adequately trained in the handling of these devices (see Appendix IV, no. 1.3.10. of the Directive 2006/17/EC).

Sterile disposable instruments must be used for tissue procurement procedures associated with potential risk of exposure to transmissible spongiform encephalopathy (TSE) pathogens. If this is not possible, the instruments used must be reprocessed/sterilised in accordance with the procedures recommended by the RKI for suspected occurrence of Creutzfeldt-Jakob disease [12]. In principle, and to reduce or eliminate risk of transmission of prion diseases, the donor exclusion criteria specified in Appendix I, no. 1.1.4. of the Directive 2006/17/EC must be taken into account.



5.4. Air Ventilation Requirements for Tissue Procurement Units

The air ventilation requirements for tissue procurement facilities depend on the extent of invasiveness, i.e. on the potential risk of the procedure (for living donors) and on the degree of contamination of the body region (for living or non-living donors) from which the tissue is to be harvested.

The requirements for rooms where tissue is procured from physiologically germ-free and potentially contaminated regions of the body of living donors are the same as those for operating theatres (room class I as specified in DIN 1946, Part 4 [11]). The same conditions are also recommended for tissue procurement from physiologically germ-free regions of a deceased donor to prevent microbial contamination of the donated tissue.

An air ventilation system is not necessary if the tissue procurement from physiologically germ-free regions of post-mortal donors is performed with aseptic harvesting techniques, and if the procured tissue is tested to detect microbial contamination using a validated test method, or if the tissue will be sterilized using a validated sterilization process. Bone, for example, may be sterilized after procurement. Correct execution of this process must be documented in each case.

Methods for sterility or bioburden analysis of procured tissue must be appropriate for the tissue tested. Swab or contact testing from the surface of large pieces of tissue, in particular, are not sufficient [13]. In these cases, rinsing/washing or enrichment processes/analyses should be applied. It may also be necessary to determine the initial bioburden prior to performing a decontamination procedure, to ensure that the capacity of the intended decontamination process is not exceeded.

An air ventilation system to prevent infection is not required for tissue procurement from physiologically colonized body areas of deceased donors. The same applies, under the same conditions, for living donors, provided that the donor is not subjected to a higher harvesting or infection risk according to the current understanding of medical science and technology.



5.5. Commissioning, Service and Repair

The qualification, i.e. the technical and hygienic acceptance inspection, of air ventilation systems in operating theatres and other rooms designated for tissue procurement must be performed prior to initial operation, based on standard requirement specifications and taking into account valid regulations (DIN 1946, Part 4 or alternatively VDI 2167-1). Testing the tightness of the filters, leak tests and requalifications should be repeated regularly, at least every two years or following manipulation of the end filter.

Devices, instruments and other equipment belonging to a procurement organisation, which are crucial for the safe performance of a tissue procurement, must undergo regular preventive maintenance according to the manufacturer's specifications (see Appendix IV, no. 1.3.8. of the Directive 2006/17/EC). This equipment should be included in a maintenance plan to assure quality and traceability. The maintenance plan must indicate how often and at what intervals the equipment must be serviced, and specify the name of the service technician. Sensitive and frequently used devices (e.g. autoclaves for the sterilization of surgical instruments) must be serviced more frequently. Metrological devices with a precision measuring function must be calibrated. Maintenance work must be carried out by qualified technicians.

If there is no qualified staff person to carry out certain maintenance work in the procurement organisation, service contracts must be set up with external professional companies. The procurement organisation must audit the external company and check the qualifications of the personnel before placing the service order. Time intervals and the scope of the service must be stipulated in the service contract. The documentation pertaining to the service work must be archived. The responsible medical person in the procurement organisation must ensure that the maintenance is performed according to schedule and within the required scope.

Apparatus, devices and surgical instruments, as well as other instruments crucial for the safety and quality of the tissue procurement, instrument sets and equipment that are no longer in functional condition must be repaired or replaced. New and repaired equipment crucial for tissue procurement must be tested prior to installation or must undergo operational qualification tests or revalidations before they are put into operation again.



6. Hygiene

6.1. Sanitary Measures and Hygiene Plan of Procurement Organisations

According to the law concerning prevention and control of infectious diseases in humans (Infection Protection Act – IfSG), a hygiene plan must exist in hospitals and facilities for inpatient and outpatient surgeries (hygiene plan in accordance with § 36 para. 1 IfSG or Accident Prevention Regulation Healthcare Service (UVV), BGV C8 (formerly VBG 103) (Appendix 2)) [14]. According to this provision, procurement organisations must also have a regularly updated hygiene plan.

The required hygiene plan is based on the recommendations of the RKI and consists of individual discipline- and activity-related hygiene instructions (The requirements for prevention of infection in patient care, diagnostic and therapy, cleaning, disinfection, sterilization and for the operational organization in special divisions, can be found on the RKI homepage, www.rki.de, under Prevention of Infection ▶ Hospital Hygiene ▶ Commission for Hospital Hygiene and Infectious Disease Prevention). The hygiene plan must be in writing and must be followed to protect the living donor, the harvested tissue (whether from living or deceased donors) and the personnel.

Identical requirements for hygiene apply for outpatient or inpatient invasive procedures, and thus also for outpatient or inpatient tissue procurement [11].

An effective sanitation plan takes into account all necessary technical and operational-organisational measures. In addition to prevention of microbial infection, the plan should also have the objective of preventing adverse effects arising from necessary cleaning, disinfection, sterilization, supply and disposal activities, including the regular sensitisation of the personnel to good hygiene practices.

The necessary hygiene measures must be described separately for each field of activity. The hygiene plan must clearly stipulate which activities must be performed, how and by whom they are to be performed, and who is the person responsible for monitoring and supervising the various activities in the procurement organisation. The controlled area comprises personal hygiene, sanitation in the areas where tissue is procured, including microbiological monitoring, and the special sanitation requirements for the respective tissue procurement. Special requirements for the hygiene plan can also be determined together with the manufacturer and/or the processing company.



The execution of the sanitation activities, especially the daily cleaning and disinfection of the rooms for tissue procurement, must be appropriately documented.

The monitoring of and compliance with the hygiene plan in a clinical facility is normally done by a medical doctor, who coordinates this with the respective trained personnel (hygiene specialist, hospital hygienist). In a procurement organisation without additional hygiene personnel, the responsible medical person is in charge of all necessary sanitary measures.

6.2. Special Sanitary Measures by Harvesting Personnel and for Donors Before, During and After Tissue Procurement

The RKI recommendations which are described in communications issued by the Commission for Hospital Hygiene and Infectious Disease Prevention [11] apply here as well. They contain detailed requirements on the sanitary activities to be carried out.

If tissue is procured from non-contaminated or minimally contaminated regions, the same conditions apply as for surgery (special clothes, pre-operative hand disinfection, sterile gloves and surgical gowns, including face mask, surgical cap, shoes, and thorough disinfection of the skin in the area where the tissue procurement is performed).

If tissue is procured from physiologically contaminated regions, the procedure must be performed using sterile instruments and (at least) with sterile gloves and a face mask. The same conditions apply for tissue procurement from deceased donors, in which the surgical intervention must be limited to the site of the tissue/cell harvest. A localised disinfected region covered with sterile sheets must be prepared (see Appendix IV, no. 1.3.3. of the Directive 2006/17EC).

The body region concerned must be disinfected/made antiseptic prior to performing an invasive procedure through the skin and mucosa. The same requirements apply for procurement of skin and mucosal cells.

In addition, and based on Appendix IV, no. 1.3.7. of the Directive 2006/17/EC, procedures and protocols must be available which minimise the risk of a contamination of tissue and/or cells by personnel with a potentially contagious disease.



It is therefore recommended that the personnel involved in tissue procurement are subjected to a regular health screening. The responsible medical person of the procurement organisation must decide on the action to be taken in the case of personnel who could pose an unjustifiable microbiological risk.

7. Personnel

7.1. Personnel in Key Positions and Assisting Personnel

§ 8 para. 1 sentence 1 no. 4 TPG stipulates that the procurement of human tissue from a living donor for the manufacture of a drug – including the manufacture of a test medication for use in a clinical trial (§ 3 paragraph 3 GCP-V) – may only be performed by a licensed medical doctor. In contrast to this, § 3 paragraph 1 sentence 2 TPG stipulates that the procurement of human tissue from deceased donors can also be performed by qualified personnel with prior instruction from a medical doctor. The medical doctor is the responsible signatory for the procedure.

In the event of unexpected problems during the tissue procurement (e.g. post-mortem donors with previously unknown intestinal injuries), the medical doctor in charge of the procurement must decide whether or not the donor is still qualified.

There must be a sufficient number of assisting personnel with adequate qualification for carrying out the respective procurement procedure to ensure a safe, problem-free procurement procedure. Detailed, up-to-date, written job descriptions for these personnel must be filed in the quality manual. These job descriptions may be written in the form of SOPs. The assisting personnel must be able to understand their assigned scope of duties, authorities and responsibilities.

7.2. Training and Training Certificates of Personnel Involved

Persons who procure tissue must receive adequate specialised training for this procedure prior to their first autonomous tissue procurement. The training can be conducted by an authorised trainer sent by a manufacturer with a manufacturing licence according to § 13 AMG, or by the processing company with a permit according to § 20c AMG, or by a member of the medical personnel from the procurement organisation who is already trained and qualified for the procedure and the harvesting technique (see Article 2 paragraph 2 of the Directive 2006/17/EC).



The training must cover all theoretical and practical aspects, from donor selection, donor information, surgical technique used for tissue procurement, to the identification, packaging, storage and tracking of the harvested tissue. This also comprises all relevant safety, hygiene, health and documentation regulations, as well as relevant ethical, regulatory and legal provisions.

Surgical and harvesting techniques must be explained and demonstrated in detail and the trainee should practise the techniques, on a mannequin, if necessary. The relevant training aids and documents must be given to the trainee.

Regular skills development training should also be provided for persons who procure tissue (i.e. medical doctors and other qualified personnel who perform tissue procurement on deceased donors). This is particularly important if there are changes in the techniques and methods for tissue procurement and also to allow procurement personnel to remain current with advancements in medical science concerning, for example, inclusion and exclusion criteria of tissue donors, and hygiene.

Personnel who assist during tissue procurement must also receive regular training, which must include all relevant aspects of the QA system. The responsible medical person is responsible for the training of assistant personnel. Training activities must be documented, dated, and signed by the trainer, and then archived.

7.3. External and Additional Personnel

If the procurement organisation employs external personnel for certain tasks or operations, e.g. for the cleaning and disinfection of the operating rooms, it must ensure that such personnel are qualified to perform their assigned tasks. Relevant service contracts must be signed with the service providers. Additional or external personnel must also receive regular training, especially with regard to hygiene requirements in the procurement organisation.

8. Inspections and Audits

8.1. Self-inspections

The procurement organisation is advised to carry out regular self-inspections. This should be done at least every two years. An internal audit plan must be prepared, and the results of each internal audit must be documented in writing.



Any deficiencies identified must be documented in writing and rectified immediately. Procurement organisations can also engage qualified companies to conduct the audit. In this case, the directives of the § 9 AMWHV must be observed, which require the signing of binding contracts.

8.2. Audit by the Manufacturer or the Processing Company

The manufacturer or the processing company can audit the procurement organisation prior to the application for a permit for tissue procurement, or as part of an already granted permit. The procurement organisation normally will receive an audit checklist with questions it must answer. This can be followed by an on-site physical inspection to verify the procurement organisation's answers to the checklist questions.

8.3. Official Inspections

Official inspections can be conducted announced or unannounced. If announced, the authority will normally inspect the main QA documents of the procurement organisation first. The authority can then decide to follow up with a physical inspection prior to granting the permit (§ 20b para. 1 sentence 4 AMG). An audit report must be drafted and sent to the procurement organisation (§ 4 paragraph 7 AMGvV). Any faults and deficiencies identified must be rectified by order from the authority.

9. Conditions for the Procurement of Human Tissues or Cells

9.1. Legal Provisions

Human tissue as specified in § 1a no. 4 TPG, and thus also individual cells for human application, including for the purpose of drug production or trial medication, can be procured from deceased donors (e.g. eye corneas, skin, bones, blood vessels, and cardiac valves) or from living donors (e.g. bone marrow, femoral heads during the implantation of a primary hip joint prosthesis, and chondral tissue for autologous chondrocyte transplantation) for directed or non-directed donation (as related to the recipient).



The relevant European legislation is contained in Article 2 of the Directive 2006/17/EC. The national provisions in force in response to the European legislation for tissue procurement on deceased donors are specified in Subdivision 2 of the TPG in §§ 3 to 7 TPG and for living donors in Subdivision 3 of the TPG in §§ 8 to 8c TPG. In addition, compliance is required with the directives of § 8d TPG and the provisions of § 9 TPG.

According to § 8d TPG, the procurement organisation shall undertake to:

- (1) abide by the requirements for the procurement of tissue according to state-of-the-art medical science and technology, especially in regard to donor identification, the harvesting procedure and the donor documentation,
- (2) ensure that tissue is procured only from donors who have undergone a thorough state-of-the-art medical examination with the result that the donor is medically suitable,
- (3) ensure that state-of-the-art laboratory analyses are performed for donors in a suitable analytic laboratory according to § 8e TPG,
- (4) ensure that the tissue for reprocessing, processing or further processing, preservation or storage is only approved and released, if the medical examination according to (2) and the laboratory analysis according to (3) have confirmed that the tissue is suitable for this purpose,
- (5) take appropriate measures to ensure the necessary medical care for living donors before and after the procurement,
- (6) ensure quality assurance for all actions from (2) to (5).

According to § 9 para. 2 TPG, the possible procurement and transplantation of a transplantable organ has priority over the procurement of tissue. A tissue procurement may not delay or hinder an organ transplant. Tissue from a potential donor of transplantable organs according to § 11 para. 4 sentence 2 TPG may only be procured if the person in charge of the coordinating unit has declared that the procurement or transplant of transplantable organs is not possible or is not delayed or hindered by the tissue procurement (see also § 11 para. 4 sentence 3 and 4 TPG).



9.2. General and Special Selection Criteria for Tissue Donors

Suitable inclusion and exclusion criteria for tissue donors must comply both with the safety requirements for donors and with the safety and quality requirements for recipients. This means that the life or health of living donors may not be threatened by the tissue procurement and that the procured tissue or its reprocessed forms is able to achieve the desired therapeutic effect without disproportionate side effects for the recipient after transplant or administration (see also § 8 para. 1 sentence 1 TPG).

In reference to the introductory text of Appendix I of the Directive 2006/17/EC, the selection criteria for donors are therefore based on a risk analysis for the use of the specific tissue. Indications for such risks must be determined through a physical examination, a patient history, biological analyses, the post-mortem examination of deceased donors and other suitable examinations and analyses.

If the donation cannot be conclusively approved based on a documented risk analysis conducted by the doctor in charge of the tissue procurement, the donor must be excluded if one of the conditions or exclusion criteria stated in Appendix I (for donors of tissue and cells, except donors of reproductive cells) or Appendix III (for donors of reproductive cells) of the Directive 2006/17/EC applies.

If additional or special selection criteria exist for donors of tissue, these specifications or instructions must also be taken into account when assessing donor suitability. Examples of such additional or special criteria include, in Germany, the provisions of the already mentioned Transplantation Act, the regulations of the Federal Medical Council for haemotherapy, bones, eye cornea and other tissues and cells (see also chapter 19.2. of the GPP-Guidelines), the recommendations of medical expert groups such as the Joint Advisory Board of the German Societies for Traumatology and Orthopaedic Surgery on autologous chondrocyte transplantation, or criteria from the manufacturers or processing companies to which the procured tissue is supplied.

The respective medical expert groups are also encouraged to define additional tissue type-based selection criteria for donors and/or recipients, if such regulations or recommendations have not yet been formally established, but are supported by current scientific evidence. Such additional regulations or recommendations may be specific to certain tissues or cells, formulations produced from them, or their indication-related therapeutic applications.



Inclusion and exclusion criteria for tissue donors, including the necessary laboratory tests and release procedures must be defined in the QA system of the procurement organisation, with special attention to the relevant legal provisions and regulations, especially § 8d TPG and the latest advancements in medical science and technology.

9.3. Laboratory Analyses to Ascertain the Suitability of the Donor

The necessary laboratory tests as part of the risk analysis and the exclusion of a donor, as well as the requirements on how these procedures should be conducted, are described in Article 4 of the Directive 2006/17/EC together with Appendices II and III for living and deceased donors, autologous and allogeneic donation, and for donation of reproductive cells (including partner and third party donation).

Biological tests are required for donors (except reproductive cell donors) according to Article 4 para. 1 and Appendix II, no. 1 of the Directive 2006/17/EC. These tests include serological tests for HIV-1, HIV-2, HBV, HCV and syphilis. Additional laboratory tests (e.g. RhD, HLA, malaria, CMV, *Toxoplasma*, EBV, *Trypanosoma cruzi*) may be required in certain situations, depending on the medical history of the donor and the characteristics of the tissues or cells donated.

§ 8e TPG stipulates that the necessary laboratory tests for tissue donors according to § 8d para. 1 sentence 2 no. 3 TPG, read together with Article 4 of the Directive 2006/17/EC, may only be performed by an analytical laboratory licensed according to § 20b para. 1 AMG, or which operates under contract to a manufacturer or processing company with a permit to engage the services of the analytical laboratory under contract (§ 20b para. 2 AMG).

The analytical laboratory must have a QA program and must ensure the quality of the laboratory tests, as prescribed in § 8d para. 1 sentence 2 no. 3 TPG. The applied laboratory test methods must be validated according to Appendix II, no. 2.1 of the Directive 2006/17/EC in regard to the intended purpose and taking into account state-of-the-art science and technology. Critical test methods must be evaluated on a regular basis to ascertain whether they are still valid or whether they need to be revalidated.



Laboratory tests must be performed according to written SOPs established in advance (test instruction) and must be fully recorded (test record). Any deviations from the procedure or the specification must be documented and thoroughly analysed. The person in charge of laboratory testing must confirm that the test was performed according to specification, and sign and date the test report.

Laboratory tests to establish the suitability of a donor can also be performed by the manufacturer or processing company, provided that this is stipulated in a contract with the procurement organisation (see also chapter 3.3 of the GPP-Guidelines). If the analytical laboratory has no own licence according to § 20b para. 1 AMG, the manufacturer or processing company must ensure quality according to § 20b para. 1 sentence 3 no. 4 AMG for the mandatory laboratory tests required by § 8d para. 1 sentence 2 no. 3 TPG.

10. Donation and Procurement Procedures

10.1. Consent and Donor Identification

According to § 8 para. 2 sentence 4 TPG, the medical doctor must confirm and document, prior to tissue procurement from living donors, that he/she has the donor's consent according to § 8 para. 2 sentence 1 and 2 TPG. According to the Appendix IV, no. 1.1.1. of the Directive 2006/17/EC, reliable donor identification must be documented as well.

Donor information, especially as part of Good Professional Practice, is very important for obtaining the donor's consent. § 8 para. 2 sentence 1 TPG therefore stipulates very clearly that a medical doctor must inform the donor in easy-to-understand language about:

- (1) the purpose and the type of intervention,
- (2) the preliminary laboratory tests and the donor's right to be informed about the results,
- (3) the measures taken for the safety of the donor, as well as possible effects of the intended procedure on the donor's health, including short-term and long-term effects, potential severity, and extent,
- (4) doctor-patient confidentiality,



- (5) the anticipated success of the tissue transplantation and other circumstances that he/she deems important for the donation,
- (6) the collection and use of personal data.

Another important aspect of the information to be given to the donor is the fact that a tissue extraction – even if it is performed by a medical doctor using state-of-the-art equipment and know-how – represents *de facto* bodily harm according to the statutes of the law. Therefore, to perform tissue procurement legally, the donor must have given his/her consent in advance.

An explanation in writing using one of the frequently used information leaflets alone does not satisfy the legally required form of communication of information. Information must therefore be communicated directly by the doctor to the patient. This personal meeting gives the donor the opportunity to ask questions. His/her questions must be answered truthfully and in detail. Potential risks must be mentioned openly. The donor must be informed that his/her consent is the prerequisite for the tissue procurement.

If donor and recipient are one and the same person, alternative forms of treatment may have to be addressed (this is also the case for recipient information, when donor and recipient are not identical). This applies in particular for alternative methods with similar therapeutic efficacy, but lower potential risk to donors and recipients.

After the informative meeting, the donor must be able to weigh the “pros and cons” of the procedure by him/herself, thereby exercising his/her right of self-determination in an appropriate manner. According to Good Professional Practice, the donor must be granted sufficient time to think about and assess the information given by the doctor. The donor should be able to make his/her decision without pressure. The time needed to reflect depends on the individual situation and the potential risk involved.

The informative discussion must be held when the donor is alert and mentally fit to make decisions. If the donor is already sedated, he/she is no longer in full possession of his/her mental capabilities and is not able to make decisions.



A competent medical doctor, who has expertise regarding the relevant tissue procurement, must provide the donor with information about the tissue procurement process. In cases of tissue procurement from living donors for allogeneic use, (with the exception of allogeneic bone marrow donation), the donor must be informed in the presence of a second medical doctor according to § 8 para. 2 sentence 3 TPG.

The presence of a second medical doctor during the informative meeting is not, however, required for tissue procurement that is part of a medical therapy (§ 8b TPG – e.g. femoral head extraction during the primary implantation of a total hip prosthesis) and for the removal of tissue for re-transplantation (e.g. § 8c TPG – autologous chondrocyte transplantation).

It is not necessary for the doctor who has explained the procedure to also perform the subsequent tissue procurement. Nurses are not allowed to provide information. The consent is considered to be null and void if the information provided was incomplete, inaccurate, or was given after the procurement procedure. Tissue procurement without the donor's consent is ethically incorrect, illegal and must be avoided. It is therefore advisable to use standard information checklists, to ensure that all aspects and risks of the donation are covered, and no important information is left out. If a donor is not fluent in the German language, a qualified translator must be called in to assist during the informative meeting.

Furthermore, according to Appendix IV, no. 1.1.2. of the Directive 2006/17/EC, it is required that a living donor confirms that he/she has provided all data in connection with the tissue donation to the best of his/her knowledge and ability. § 8 para. 3 sentence 1 TPG stipulates that tissue procurement is only permissible if the donor has consented to the medically recommended aftercare.

According to § 8 para. 2 sentence 4 TPG, the consent for donation must be documented in writing and must be signed by the donor or his/her legal guardian, as well as by the doctor who informed the donor about the procedure and, if applicable, the signature of the second doctor. The document must be dated on the day of the informative meeting. There must be insurance covering procurement procedure risks, and the informed consent document must provide detailed information about which risks are covered. The donor can revoke his/her consent either verbally or in writing.



Bone marrow is the only tissue that can be harvested from donors who are minors, and only if additional requirements, such as those specified in § 8a TPG, are met. The legal guardian of an underage donor must be informed in the same way as described earlier. The underage donor must also be informed, provided his/her age and mental maturity permits it. His/her refusal of the procurement procedure must be taken into account.

In Germany, tissue procurement from deceased donors is only allowed if the patient has been declared brain-dead in accordance with the relevant regulations of the German Federal Medical Council (§§ 3 paragraph 1 sentence 1 no. 2, 16 para. 1 sentence 1 no. 1 TPG). Otherwise, deceased donors can only be accepted as tissue donors as specified in § 4 TPG. According to § 4 TPG, tissue procurement is only possible in cases in which the donor has given his/her written consent. If no such consent and no written objection from the potential donor are available, the donor's next-of-kin (§ 1a no. 5 TPG) must be asked if he/she is aware if the deceased relative had pledged his organs. If this is not the case, the procurement procedure can only proceed if a medical doctor has informed the next-of-kin about the possibility of an organ donation and if this has been approved. If both organ and tissue procurement are feasible, the two consents are obtained at the same time (one-step information). The next-of-kin must be made aware that his/her decision must reflect the likely wish of the deceased. During the interview, the doctor must ascertain whether the next-of-kin has had personal contact with the deceased within two years prior to his death. If the deceased person had requested someone other than the next-of-kin to make decisions regarding organ and/or tissue donation, then he/she will replace the next-of-kin.

The stipulations of the § 4a TPG apply for the procurement of tissue from non-living foetuses and embryos.



10.2. Donor Evaluation (This Section Does not Apply for Partner and Autologous Reproductive Cell Donations)

Part of the mandatory requirements for state-of-the-art procurement procedures according to § 8d para. 1 sentence 2 no. 1 TPG, read together with Appendix IV, no. 1.2.1. of the Directive 2006/17/EC, stipulate that an authorised person must survey and document the relevant medical and functional data for donor evaluation according to chapter 11 (Donor Documentation) of these GPP-Guidelines.

A variety of sources are used for the collection of these data, at least one of which must be the interview with the donor, if the donor is alive. Additional sources of information include the following (see Appendix IV, no. 1.2.2. of the Directive 2006/17/EC):

- (1) the donor's patient file,
- (2) if the donor is deceased, an interview with a person who knew the donor well,
- (3) an interview with the doctor who treated the donor,
- (4) an interview with the donor's family doctor,
- (5) the autopsy report.

A physical examination also must be performed on the deceased donor and, if justified, on the living donor, to identify potential contraindications or other factors that could exclude the donor or that would require review, based on the medical and personal history of the donor. A qualified member of a medical profession must review and evaluate the suitability of the donor, based on the complete donor file and taking into account the regulations of the Directive 2006/17/EC (Appendix IV, no.1.2.4.). A written report of this evaluation, signed and dated by the medical professional, must be prepared.

10.3. Tissue Procurement Procedures

The respective procurement procedures must match the type of donation and the donated tissue. According to the requirements of Appendix IV, no. 1.3. of the Directive 2006/17/EC, the applied procurement techniques and methods must ensure the health and safety of the living donor and protect those properties of the tissue which are necessary for their intended clinical use.



The procurement procedure must also minimize the risk of microbial contamination or any other potentially damaging contamination, especially if the tissue and cells cannot be sterilised afterwards (see 2006/17/EC, Appendix IV, no. 1.3.2.).

Whether the donor is living or deceased, the procurement and all other related procedures must be performed with due medical care and diligence, to maintain the dignity of the donor. As regards deceased donors this means that the body must be restored as nearly as possible to its original anatomical form as soon as tissue or cells have been procured (see 2006/17/EC, Appendix IV, no. 1.3.5.). The body of the donor must be handed over to his/her next-of-kin for burial in a dignified fashion. The next-of-kin must be allowed to see the body before it is transferred to the mortician (§ 6 para. 2 TPG).

Other requirements for the procurement of tissue from living or deceased donors, and regarding equipment, room requirements, sanitation and manpower requirements, are described in chapters 5 to 7 of these GPP-Guidelines.

10.4. Procurement Instructions and Procurement Protocol

Part of the requirements for state-of-the-art procurement procedures according to § 8d para. 1 sentence 2 no. 1 TPG, which must be complied with, is Article 2 paragraph 5 of the Directive 2006/17/EC, which stipulates that tissue procurement, including all measures that are meant to keep the tissue in a usable condition, its labelling and transportation, must be carried out according to a documented SOP (procurement instruction) and in keeping with the conditions stated above, and in compliance with Good Professional Practice.

For tissues or their formulations which have been approved according to § 21a AMG, the procurement instruction must conform with the approval documentation. The procurement instruction must, at minimum, comply with the regulations on:

- (1) identification and determination of the suitability of the donor,
- (2) procurement of the tissue and handling of the procured tissue, including the equipment used,
- (3) procedures for procurement and for the prevention of microbial or other contamination during procurement, as well as other measures to minimize the contamination of the product, as necessary,



- (4) (for non-living donors) details about the procurement site and necessary conditions at the site, if located outside the procurement organisation, as well as documentation of the period between time of death and tissue procurement,
- (5) requirements for the tissue or organ containers, and the chosen storage and transport solutions,
- (6) identification of the donations,
- (7) conditions for possible intermediate storage of the donations pending transportation and further processing.

The tissue procurement must be performed according to the procurement instruction and, notwithstanding the documentation duties as per § 8d para. 2 TPG, must be thoroughly recorded (procurement protocol). Any deviations from the procurement instruction or its specifications must be documented and thoroughly analysed. The person in charge of the tissue procurement must confirm that the harvest was performed according to the procurement instruction, and sign and date the procurement protocol.

In addition, any adverse event during the procurement, which has caused harm or could have caused harm to a living donor, or which could adversely affect the safety and quality of the procured tissue, as well as the result of any investigation to determine the cause of a problem, must be documented and reviewed by the responsible medical person (see also chapters 14 and 15 of the GPP-Guidelines).

11. Donor Documentation

According to § 8d para. 1 sentence 2 no. 1 TPG for the compliance with requirements for state-of-the-art donor documentation, read together with the Appendix IV, no. 1.4.1. of the Directive 2006/17/EC, a file must be created for each donor which includes the following data:

- (1) personal data of the donor (first name, surname and date of birth). If both mother and child are involved in the donation, include the name and date of birth of the mother and the name, if any, and date of birth of the child,
- (2) age, gender, medical and lifestyle history (sufficient information must be collected to allow the application of the exclusion criteria, if necessary),
- (3) medical report of a physical examination, if applicable,



- (4) haemodilution formula, if applicable (see also Appendix II, no. 2.3. of the Directive 2006/17/EC),
- (5) clinical data, results of laboratory tests and other studies,
- (6) autopsy report, if an autopsy was performed (a preliminary verbal autopsy report must be recorded on tissues and cells which are unsuitable for long-term storage),
- (7) for donors of haematopoietic progenitor cells, the suitability of the donor for the chosen recipient must be documented. If donor and recipient are not genetically related and if the organisation responsible for the procurement has only limited access to the recipient data, the transplantation facility must be provided with the relevant donor data to allow confirmation of suitability.

If the tissue is not processed in the same department or facility in which it was harvested, a procurement report must be prepared, in addition to the procurement protocol and donor file, and sent to the manufacturer or the processing company. The procurement report must confirm the donor history and the donor suitability evaluation as required by regulations and must, in accordance with Appendix IV, no. 1.4.2. of the Directive 2006/17/EC, contain at least the following additional information:

- (1) identification, name and address of the processing company to which the tissue or cells are supplied,
- (2) donor identification data (including details specifying how the donor was identified and who performed the donor identification),
- (3) description and identification of procured tissues or cells (including tissue or cells extracted for testing purposes),
- (4) identification of the person responsible for this procurement, including his/her signature,
- (5) date, time (including start and end times, if necessary), place of the procurement, the procurement method (SOP) used, including any adverse events, and, if necessary, ambient conditions at the procurement site (description of the area where procurement took place),
- (6) for deceased donors, description of the conditions under which the body was stored (e.g. refrigerated or not), refrigeration start and end times, if necessary,
- (7) ID/batch numbers of reagents and transport solutions used,



- (8) for deceased donors, the place and time of death, if this information is available.

For semen collection, the procurement report must also specify if collection was performed at home. If so, the report must state only:

- (1) name and address of the tissue establishment to which the semen will be sent,
- (2) donor identification,
- (3) if possible, date and time of procurement (not mandatory).

Medical care facilities must ensure, according to § 13a TPG, that each transplanted tissue is documented by the handling doctor, or is documented on his/her orders and under his/her responsibility, for tracking purposes and for purposes of risk recording, according to the regulations of the German Medicines Act or other legal provisions. An ordinance for this requirement based on the § 16a TPG is still pending. Other general and special requirements for the documentation are described in chapters 4.1. and 4.2. of these GPP-Guidelines.

12. Packaging, Storage and Identification of Procured Tissue

According to Appendix IV, no. 1.5. of the Directive 2006/17/EC, all harvested tissues must be stored and packed after procurement to minimise risk of contamination. The containers used must be suitable for storage and transportation of the relevant biological material. The containers must protect and preserve the safety and quality of the tissue contained therein.

Tissue must be stored under conditions and at temperatures that maintain its characteristics and biological functions. Maximum storage periods (including transportation times) must be determined and specified. Storage for the specified duration must not result in significant deterioration in the properties of the tissue.

The transportation methods must be validated. Primary containers and materials that are in direct contact with the tissue must be qualified. Ideally, containers and materials for the primary and secondary packaging should be provided by the manufacturer or the processing company.

The packaging must also prevent contamination originating from persons responsible for packaging and transportation of the tissue (see Appendix IV, no. 1.5.1. of the Directive 2006/17/EC).



Every tissue-containing package must be labelled at the time of the procurement. Packaging and labelling procedures must be specified in written SOPs, and these procedures must be followed in actual practice.

According to Appendix IV, no. 1.6. of the Directive 2006/17/EC, the primary container holding the tissue must, as a minimum requirement, bear a label specifying the donor's identity and/or donor code, and the type of tissue within the container. If the primary container is large enough, it should bear a label including the following data:

- (1) donor identity and/or donor code, and type of tissue,
- (2) date and, if possible, time of procurement,
- (3) hazard warnings,
- (4) nature of any additives (if used),
- (5) in the case of autologous donation the label must state "for autologous use only"; and in the case of directed donations, the label must identify the intended recipient.

If the primary container cannot bear a label large enough to include the information specified in points (2) to (5), above, this information must be included in an accompanying document attached to the primary container. Likewise, tissue or blood samples included in the container for testing must be adequately labelled to enable them to be assigned to the correct donor and to prevent mix-ups. Specific information about time and place of tissue procurement must also be included on these samples.

If the tissue is transported by a third party (e.g. a forwarding company), the Appendix IV, no. 1.7. of the Directive 2006/17/EC stipulates that each transport container be labelled with, at minimum, the following information:

- (1) "Caution", "Tissues and Cells" and "Handle with Care" labels,
- (2) identification of the establishment from which the package originates (including address and telephone number) and name of a person at the originating establishment to be contacted in the event of problems,
- (3) identification of the processing company, tissue bank, or other destination establishment (including address and telephone number) and name of a person to be contacted to take delivery of the container,
- (4) date and time of the start of transportation,
- (5) specifications regarding the transportation conditions necessary to maintain safety and quality of the tissue or cells,



- (6) the additional text: "Do not irradiate",
- (7) if it is known that the donor is positive for a relevant infectious disease marker, the following text must be added: "Biological Hazard",
- (8) in the case of autologous tissue/cell donations, the following text must be added: "For autologous use only",
- (9) any additional specifications regarding storage conditions (e.g. "Do not freeze").

13. Transport

The transport of procured tissue to the manufacturer or processing company must take place under safe and controlled conditions which ensure preservation of cell and tissue properties necessary for the intended clinical application, and do not risk contamination. The chosen modes of transportation must be suitable for the biological and logistic requirements, and must be specified in writing in accordance with Article 2 paragraph 5 of the Directive 2006/17/EC. Transport specifications must determine the type of transport container and the way it is identified, as well as the inclusion of samples, if any, and the procurement report to the processing company.

The operational validation of tissue transport must take into consideration requirements relating to the container internal temperature, environmental temperature, as well as other biological, chemical and physical parameters. Seasonal temperature fluctuations must be taken into account, if applicable. If, for example, the tissue must be maintained within a particular temperature range during transport, it is recommended to place a suitable temperature sensor inside the package, to monitor and document internal temperatures. Transport times must be specified in the predetermined terms and conditions of transport, which ensure the retention of the necessary cell and tissue properties.

Dates and, if relevant, times of package collection at the procurement organisation and delivery to the manufacturer or processing company, must be documented. During transport, access to the package and its contents by unauthorized third parties must be prevented. If necessary, a sealable outer transport container must be used. Variances or incidents occurring during transport must be reported to the procurement organisation and the manufacturer or processing company.



Transport contracts must be concluded with qualified forwarding companies. The forwarding company must ensure full compliance with the specified, validated transport conditions.

Procurement organisations can put the manufacturer, the processing company, or third parties in charge of transportation of procured tissue or cells. In such cases, written agreements must be established, specifying the responsibilities of the third parties and detailed procedures to be followed (see also chapter 3.3.).

14. Activities After the Occurrence of Suspected Serious Adverse Events or Serious Adverse Reactions

Serious adverse events are defined in the TPG (§ 1a no. 10) and in the AMG (§ 63 c paragraph 6). The TPG explains in more detail that any faulty identification or mix-up of reproductive cells or embryos during a medically assisted fertilisation must be considered as a serious adverse event.

Serious adverse events in procurement organisations are defined as any events associated with the procurement, storage or delivery of the tissue which can lead to certain unwanted consequences.

Serious adverse reactions are also defined in the TPG (§ 1a no. 11) and in the AMG (§ 63c para. 7). As far as procurement organisations are concerned, these are unintentional reactions, including transmission of a disease to the donor, which occur in connection with tissue procurement and which can lead to certain unwanted consequences. The recipient can also suffer serious adverse reactions in connection with the administration of the tissue formulation.

Immediate action is necessary upon detection or suspicion of serious adverse events or adverse reactions during procurement and also during administration of tissues or their preparations. This is the responsibility of the medical doctor in charge of the specific procedure, for example, procurement.

If necessary, the doctor in charge will immediately seek the advice of the responsible medical person to identify and take the actions needed to prevent or minimise harmful effects to all potentially affected patients and persons. The QA system of the procurement organisation must include appropriate instructions for staff in these situations (see also chapter 15 of the GPP-Guidelines).



Implementation of these instructions in the event of a known or suspected serious adverse events or serious adverse reactions must be monitored by the responsible medical person.

Tissue procurement may not be performed if the procurement organisation would be unable to take appropriate remedial action to protect the life or health of the donor in response to a known or suspected adverse incident during tissue procurement.

These GPP-Guidelines do not include the reporting of suspected adverse side effects according to § 63b AMG for tissue preparations with approval requirement according to AMG. These are preparations which do not fall under the § 21a AMG, because they are processed or reprocessed with industrial methods, the main processing- or reprocessing methods are not well-known in the EU, and their efficacy and side-effects are not described in scientific study reports and literature.

15. Duty to Report

According to § 13c para. 1 TPG, tissue establishments and procurement organisations must define a tracking process that enables them to immediately isolate and exclude from delivery any tissue that may potentially cause a serious adverse event or serious adverse reaction, and to inform medical facilities and organisations responsible for human application (§ 1a no. 9 TPG) if they have been supplied with such tissue.

Medical care facilities or any other organisations responsible for human application must, immediately following identification, 1) document any serious adverse event that could have been caused by tissue procurement activities, and 2) document any adverse reaction which occurs during or after the clinical application of tissue or tissue preparations and which can be linked to their quality and safety, and 3) must notify the manufacturer or processing company which supplied the tissue (§ 13b TPG).

The owner of a permit to put a product into circulation in accordance with § 21a AMG must, as specified in § 63c para. 1 and 2 AMG, keep detailed records on every suspected serious adverse event that can affect the quality or safety of the tissue preparation, and on every suspected serious adverse reaction that influences or is caused by the quality or safety procedures involved in tissue preparation.



The permit holder must also report suspected cases immediately, i.e. within 15 days after receipt of the information, to the national regulatory authority. The German surveillance authority for these products is the Paul Ehrlich Institute (PEI) in Langen.

Regarding tissue or tissue preparations that are not subject to authorisation, the tissue establishment/bank, and the procurement organisation, must, according to § 63c para. 3 AMG, document every suspected serious adverse event that might potentially affect the quality or safety of the tissue or the tissue preparation, and every suspected serious adverse reaction which influences or is caused by the quality or safety procedures related to the tissue or tissue preparation. Such events must also be reported to the surveillance authority immediately after receiving the alert. The potential causes of the reported adverse events and reactions must be investigated and analysed, and the results reported to the surveillance authority without delay, together with the tracking activities implemented for the protection of the donor and recipient.

Specific instructions and responsibilities for record-keeping, analysis, evaluation, documentation and reporting of serious adverse events and adverse reactions must be defined in the QA system of the procurement organisation, taking into consideration the respective, valid legal provisions.

The responsible medical person in the procurement organisation has the duty to report identified or suspected serious adverse events or unwanted reactions.

According to § 8d para. 3 TPG, a procurement organisation must document its activities, must publicly disclose these documents, and must also send an annual report to the Paul Ehrlich Institute.

16. (Selected) Literature and Comments on the Text

1. A procurement organisation according to the definition in brackets given in § 20b para. 1 AMG is at the same time a tissue bank according to TPG (§ 1a no. 8 TPG). The definition of a procurement organisation is given in § 2 no. 11 AMWHV and does not differ from the definition specified in § 20b para. 1. The reference to § 13 AMG given in § 2 no. 11 AMWHV was rendered obsolete by the Tissue Act and will be omitted in the course of the AMWHV amendments by the amending statute (as of 07.08.2007) currently available as draft statute.



2. ABl.-EC L 102, p. 48.
3. ABl.-EC L 38, p. 40.
4. Law concerning the quality and safety of human tissue and cells (Tissue Act) dated 20.07.2007, BGBl 2007 Part I, p. 1574.
5. See Bundestag printed matter 16/5443 (preliminary electronic version), for no. 30a (inclusion of § 16b TPG), p. 99.
6. See EC GMP-Guideline, Federal Gazette no. 210 dated 09.11.2006, p. 2523.
7. Gaissmaier C, Fritz J, Angele P, Niethard FU, Weise K, Bauer H, Pannenbecker A. The Tissue Act – new legal provisions for the procurement of tissue or cells for drug production. Information from the German Society of Surgery 2007; 4: 369-374.
8. Ordinance concerning the application of Good Clinical Practice during clinical trials of drugs intended for human application, Federal Gazette 2004, Part I, p. 2081, last amended with Article 4 of the VO to replace the PharmBetrV (Federal Gazette 2006, Part I, p. 2542).
9. Centres for Disease Control and Prevention (CDC). Guidelines for the prevention of surgical site infection. ICHE 1999; 20: 247-280.
10. Hansis M, Arens S. Pathophysiology of the postoperative infection of bones and soft tissue. Akt Traumatol 1996; 26: 183-191.
11. Hygiene requirements during surgery and other invasive procedures. Information from the Commission for Hospital Hygiene and Prevention of Infection at the Robert Koch Institute. Federal Healthcare Gazette – Healthcare Research – Health Protection 2000; 43: 644-648.
12. Task Force vCJK at the Robert Koch Institute (RKI): Variant Creutzfeldt-Jakob disease (vCJK). Epidemiology, identification, diagnostic and prevention with special consideration of the iatrogenic transmission through medical products, especially surgical instruments. Federal Healthcare Gazette – Healthcare Research – Health Protection 2002; 45: 376-394.
13. Veen MR, Bloem RM, Petit PL. Sensitivity and negative predictive value of swab cultures in musculoskeletal allograft procurement. Clin Orthop Rel Res 1994; 300: 259-263.



14. Law concerning the prevention and combat of infectious diseases in humans (Infection Prevention Act – IfSG). BGBl 2000 Part I, p. 1045, last amendment, Article 6 of the Tissue Act, BGBl 2007 Part I, p. 1574.

17. Abbreviations

AMG	Law concerning the trafficking of drugs (German Medicines Act)
AMWHV	German ordinance for the production of medicinal products and active substances
BÄK	Federal Medical Council
BDSG	Federal Data Protection Law
BGBl	Federal Law Gazette
BMG	Federal Ministry of Health
CMV	Cytomegalovirus
DGCH	German Society of Surgery
EBV	Epstein-Barr virus
EC	European Community
EU	European Union
GCP	Good Clinical Practice
GPP	Good Professional Practice
GMP	Good Manufacturing Practice
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
IfSG	Infection Prevention Law
PEI	Paul Ehrlich Institute
QM	Quality management
QA	Quality assurance
RhD	Rhesus factor D
RKI	Robert Koch Institute
SGB	Social security code
SOP	Standard operating procedure
TFG	Law concerning the regulation of transfusions (Transfusion Law)



TPG	Law concerning the donation, procurement and transplantation of organs and tissues (Transplantation Law)
TSE	Transmissible spongiform encephalopathy

18. Glossary

According to the term definitions given in the TPG (marked with asterisk (*)) and the Commission Directives 2004/83/EG, 2006/17/EC and 2006/86/EG:

Allogeneic use: cells or tissues removed from one person and applied to another

Autologous use: cells or tissues removed from and applied in the same person

Cells: individual human cells or a collection of human cells when not bound by any form of connective tissue

Critical: potentially having an effect on the quality and/or safety of or having contact with the cells and tissues

Direct use: any procedure where cells are donated and used without any banking

Distribution: transportation and delivery of tissues or cells intended for human applications

Donation: donating human tissues or cells intended for human applications

Donor: every human source, whether living or deceased, of human cells or tissues

*Harvest: the harvesting of organs or tissues

Human application: the use of tissues or cells on, or in a human recipient and extracorporeal applications

*Medical facility: a hospital or another facility with direct patient care, which is under constant medical supervision and management and which provides medical services

*Next-of-kin: in the order listed a) spouse or registered unmarried permanent partner, b) adult children, c) parents or, if the potential organ or tissue donor was a minor at the time of death and was cared for at this time by only one parent, a guardian or a carer, the legal guardian, d) adult siblings, e) grandparents

*Non-regenerative organs: all organs, which do not regenerate in the donor after removal



Organisations responsible for human application: a health care establishment or a unit of a hospital or another body which carries out human application of human tissues and cells

*Organs: with the exception of skin, all parts of the human body formed by different tissues which, in terms of structure, vascularisation and the capacity to perform physiological functions, form a functional unit, including organ parts and individual tissues or cells of an organ, which can be used in the human body for the same purpose as the organ as a whole

Partner donation: the donation of reproductive cells between a man and a woman who declare that they have an intimate physical relationship

Preservation: means the use of chemical agents, alterations in environmental conditions or other means during processing to prevent or retard biological or physical deterioration of cells or tissues

Processing: all operations involved in the preparation, manipulation, preservation and packaging of tissues or cells intended for human applications

Procurement: a process by which tissue or cells are made available

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

*Procured organs: heart, lung, liver, kidney, pancreas and intestine according to the organ definition, which were harvested according to § 3 or § 4 TPG

Quality system: the organisational structure, defined responsibilities, procedures, processes, and resources for implementing quality management and includes all activities which contribute to quality, directly or indirectly

Quality management: the coordinated activities to direct and control an organisation with regard to quality

Quarantine: the status of retrieved tissue or cells, or tissue isolated physically or by other effective means, whilst awaiting a decision on their acceptance or rejection

Reproductive cells: all tissues and cells intended to be used for the purpose of assisted reproduction



*Serious adverse event: any unwanted event associated with the procurement, testing, reprocessing, processing, preservation, storage or distribution of tissue that might lead to the transmission of a communicable disease, death or a life-threatening condition, a disability or the loss of functional abilities of patients or might require or prolong hospitalisation or cause or prolong a disease; a serious adverse event is also every false identification or mix-up of reproductive cells or embryos during medically assisted fertilization

*Serious adverse reaction: an unintentional response, including a communicable disease, in the donor or recipient associated with the procurement or human application of tissue that is fatal or life-threatening, causes a disability or the loss of functional abilities or requires or prolongs hospitalisation or causes or prolongs a disease

Standard operating procedures (SOPs): written instructions describing the steps in a specific process, including the materials and methods to be used and the expected end product

Storage: maintaining the product under appropriate controlled conditions until distribution

*Tissue: all parts of the human body which consist of cells, which are not organs in the sense of the organ definition, including individual human cells

*Tissue bank: a facility which extracts, analyses, reprocesses, processes, preserves, marks, packages, stores or supplies tissue for the purpose of transplantation

Tissue establishment: 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



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

*Transplantation: the use of organs or tissue in or on a human recipient

Validation (or 'qualification' in the case of equipment or environments): establishing documented evidence that provides a high degree of assurance that a specific process, SOP, piece of equipment or environment will consistently produce a product 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

19. Laws, Ordinances, Regulations, Guidelines and Recommendations that Must be Observed when Implementing the GPP-Guidelines

19.1. Laws and Ordinances

(Attention must be paid to the current valid version of each law or ordinance)

Law concerning drug trafficking (German Medicines Act – AMG)

Law concerning the donation, harvest and transplantation of organs and tissue (Transplantation Act – TPG)

German ordinance for the production of medicinal products and active substances (AMWHV)

Law concerning the regulation of transfusions (Transfusion Act – TFG)

Ordinance concerning the reporting according to §§ 21 and 22 of the Transfusion Act (Transfusion Act-Notification Ordinance – TFGMV)

Law concerning the prevention and combat of infectious diseases in humans (Infection Prevention Law – IfSG)

Federal Data Protection Law (BDSG)



Law concerning medical products (Medical Devices Act – MPG)

Medical Products Operator Ordinance (MPBetreibV)

Law concerning the liability for defective products (Product Liability Law – ProdHaftG)

Ordinance concerning the prevention of damage from ionising radiation

(Radiation Protection Ordinance – StrISchV)

Directive 2004/23/EC of the European Parliament and of the Council of 31 March 2004 setting quality and safety standards for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells

Directive 2006/17/EC of the Commission dated 8.2.2006 for the enforcement of the Regulation 2004/23/EC of the European Parliament and the Council in regard to technical requirements for the donation, procurement and testing of human tissues and cells.

19.2. Regulations, Guidelines and Recommendations of the Federal Medical Council

(Attention must be paid to the current valid version, see also: www.bundesärztekammer.de, under: Regulations, Guidelines and Recommendations)

Regulations for the extraction of blood and blood components and for the application of blood products (haemotherapy)

Regulations for the allogeneic bone marrow transplantation with non-related donors

Regulations of the Federal Medical Council for the transplantation of peripheral blood stem cells

Regulations of the Federal Medical Council for the transplantation of stem cells from cord blood (CB = cord blood)

Regulations for the management of a cornea bank

Regulations for the management of a bone bank

Regulations for the use of foetal cells and foetal tissue

Regulations for organ transplantation



Regulation for quality assurance in transplantation medicine

Regulations for quality assurance in quantitative medical laboratory tests

Regulations for quality assurance in immunohaematology

Recommendations for the further training of medical doctors

(Sample-)Professional code for German medical doctors

20. Participating Professional Associations, Authors and Acknowledgement

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