

Fig. 5. Principal document structure describing ISO 9000 Quality Management Systems.

detail (for example, no description of know-how in processing), the quality manual is very suitable for external presentation of the quality-oriented structure of the tissue bank both to the authorities and within the framework of cooperation with other tissue banks.

2. The Quality Assurance Elements in Tissue Banking

In this section, the central aspects of the individual quality assurance elements are described and a connection to tissue banking established.

2.1. Element 1: Management responsibility

A core concept of QMS according to ISO 9000 consists of the fact that the responsibility for quality lies with the management (administrators/directorship) of an enterprise (tissue bank). The management is obligated through the standard to draw up a declaration on quality policy: this is binding for staff. They are obliged to its fulfilment. In tissue banking, the high ethical demands in dealing with tissue of human origin and the state-of-the-art professional level are among the outstanding features of a quality policy.

The tissue bank management with executive responsibility shall appoint a member of the tissue bank's own management who, irrespective of other responsibilities, shall have defined authority.

Definition of management representative: "... (a) ensures that a quality system is established, implemented and maintained in accordance with this international standard (ISO 9000), and (b) reports on the performance of the quality system to the tissue bank's management for review and as a basis for improvement of the quality system."

This responsibility of a management representative may also include liaison with external parties on matters relating to the tissue bank's quality system.

Finally, the QMS is formally put into operation.

At the DIZG, this first element of the QMS includes, among others:

- the description of the institute profile,
- the fundamentals of the quality policy,
- the description of the quality policy within the framework of the surgical application of allografts,
- the organisational form of the institute,
- the stipulations on the responsibilities for securing and implementing the quality policy,
- the description of the means of implementation of the quality policy,
- the assessment of non-compliance, as well as
- the listing of the "co-valid documents".

Definition of co-valid documents: "Documents which, through mention in a QMS document, must be taken into account in the application/realisation of the document."

2.2. Element 2: Quality system

This element regulates the basis and the scope of application of the QMS of the tissue bank. The QMS stipulates the fundamentals and procedure for quality assurance. These stipulations have, at the

DIZG for example, validity for the entire institute, including the tissue bank.

The foci here are the models of quality planning, explanations of the QMS introduced and its documentation.

The QMS is based on the basic concept of the personal responsibility of the employee. With correct application, it guarantees the systematic consideration of the “quality” aspect in all phases of the processing of cell and tissue grafts and their clinical use.

The documentation of the QMS is subdivided into the following components:

- Quality Manual, QM (the QM imparts a *general* overview of the organisation of the QMS at a tissue bank);
- Quality System Procedures, QSP (QSP contain exact job descriptions, *complex processes*, statements on the interfaces and auxiliaries);
- Working Procedures, WP (WP contain regulations of *detailed instructions*);
- Standard Operation Procedures;
- Inspection Procedures, IP (IP contain regulations of individual details or detailed instructions which are related to the *carrying out of testing*);
- records and forms.

An additional focal point is quality planning. In the DIZG, everything is done through specific, systematic and timely planning of all activities, through planned training and further education and through the unequivocal establishment of responsibilities in order, in a preventative way, to avoid the emergence of faults.

The components of quality planning of the DIZG are:

- the audit plan,
- the training plan,
- the plan of institute management meetings,
- the development plans for research projects,
- quality management plans especially for allografts and cell cultures.

2.3. Element 3: Contract review

This element describes the procedure for the conclusion of contracts. This includes both contracts of the tissue bank with subcontractors for safeguarding the tissue banking as well as contracts with hospitals, clinics and other facilities which require the allografts for transplantation. The most important subcontractors for a tissue bank with regard to the maintenance of ethical foundations and quality-determining requirements are the institutions which supply tissue, test laboratories for external testing (including serological screening, sterility controls), radiation facilities, packaging manufacturers, etc. The goal is to guarantee that, in general, only fulfillable contracts are entered into by both parties – the tissue bank and the subcontractor.

The fundamentals and stipulations described in this element are effective for all offers and contracts at the DIZG for all allografts, services and co-operation agreements.

The criteria for contract review apply in particular to the co-operation agreements within the framework of the European Tissue Bank Network. These agreements are rated so highly because of the ethical code of the European Association of Tissue Banks (EATB) and the standards of the DIZG, which describe the quality requirements and test parameters to which the partners are required to adhere.

2.4. Element 4: Design control

The focus of this element is a description of the organisational structures and methodological procedures used by a tissue bank in new or further development of cell and tissue transplants and processing methods. This element is very closely connected with the principles of project management but goes much further in its description.

The established procedures guarantee a systematic, tested and documented development of new methods and preparations.

2.5. Element 5: Document and data control

The requirements of the standard in regard to document and data control intend that all documents and data must be checked and authorised as regards to content before release. In addition, it is to be guaranteed that changes to documents and data are also checked and authorised, that only current versions are in circulation and that regulations for filing (filing plan), archiving and record retention periods for the individual documents and records are defined. Within the framework of the standard series, a minimum record retention period of ten years is stipulated, assuming that the statutory regulations do not require other periods.

2.6. Element 6: Purchasing

This element describes how to ensure that purchased products meet the established quality requirements. For this purpose, subcontractors are to be assessed, detailed procurement specifications prescribed and the procured products subjected to testing. In tissue banking, the tissue-providing institutions form a focal point. In order to assess these institutions, it can be useful to carry out audits. Here too, the observance of basic ethical principles and quality assurance play a decisive role.

All cells and tissue provided to the DIZG are subjected to a receiving inspection. These inspections are carried out exclusively in accordance with an established "Receiving Control" inspection procedure by authorised persons. Only when all criteria of the receiving inspection have been met are the cells and tissue released for further processing. The results and the completeness of the receiving inspection are documented in an inspection protocol.

All purchased products (chemicals, consumable materials, etc.) are also subjected to a receiving inspection, dependant on their importance, described in the "Purchasing" quality system procedure or the carrying out of services assessed. The goal of these tests is on the one hand the possibility of quickly reacting to quality deficits;

and on the other hand, the evaluations lead to a permanent licensing of the subcontractors in the case of repeated satisfactory results.

2.7. Element 7: Control of customer-supplied product

This element raises the demand of making regulations so that customer-supplied product is not negatively affected in quality through processing. This presumes that the provided product is to be subjected to equally high standards in the receiving inspection.

This would apply, for example, when a tissue bank received an order to process femoral heads (as tissue provided from a department of orthopaedics) and to return this as processed allograft to the same department. In this case, the processing is carried out as a service.

2.8. Element 8: Product identification and traceability

This element describes the requirement that all incoming tissue be clearly identified and secured, and that the traceability from individual allograft to the donor must be guaranteed. The identification must be recorded.

In order to guarantee unequivocal identification and traceability, a seamless chain of documentation is set up for all cell and tissue grafts, which records all activities, beginning with the cell and tissue collection through all the steps of processing to the transplantation. The fundamental principle for all cell and tissue preparations is the individual donor documentation officially prescribed in the Medical Preparations Act. This is based on a "serial number" issued in the DIZG which forms the connecting link between the donor number (source of the tissue) and the batch, identification and catalogue numbers.

All products which find application in the course of processing are also identifiable through the documentation which accompanies the process, by means of batch numbers or other unequivocal identification.

In particular, in the case of complaint and in view of liability-related questions, the production of evidence that all quality assurance and ethical requirements have been met is thus given.

All heads of department of the institute are responsible for the meeting of these requirements. The concrete implementation is checked by the head of the "Quality Control" department.

2.9. Element 9: Process control

In relation to tissue banking, the planning, carrying out and documentation of measures for ensuring quality in the production of cell and tissue grafts is described in this element. Practically, all the detailed process descriptions for the production of the various allografts belong to this element. The entire methodological and graft-related know-how of a tissue bank is to be found in this element. The main areas of focus are:

- instruments of process control;
 - fault-possibility and influence analysis,
 - quality system procedures, working instructions, standard operation procedures,
 - analysis procedures for the monitoring of process ability,
 - training.
- process planning (stipulation of all processes for the production of cell and tissue grafts);
- test planning (stipulation of all tests which are required for meeting the requirements for cell and tissue grafts);
- environmental conditions (the carrying out of all process steps takes place under special environmental and working conditions, e.g. clean room conditions, laminar flow, that is to say, in accordance with a special regime which takes into account the special hygiene conditions on the basis of a hygiene regulation. These special features are fixed in the working instructions);
- documentation (the regular evaluation of the process documentation allows an assessment of the process ability of the tissue bank);

- responsibility (all staff are obliged to know and apply the regulations in force. That the staff of a tissue bank know all relevant regulations is to be documented in writing with signature!).

2.10. Element 10: Inspection and testing

With this element the standard gives the performance target that the meeting of stipulated quality requirements will be fulfilled through the carrying out of inspection and testing. Receiving inspections, intermediate testing and final inspections are to be carried out and all inspections and tests are to be documented.

The way in which the requirements of the standard could be fulfilled in tissue banking can be seen in Fig. 6.

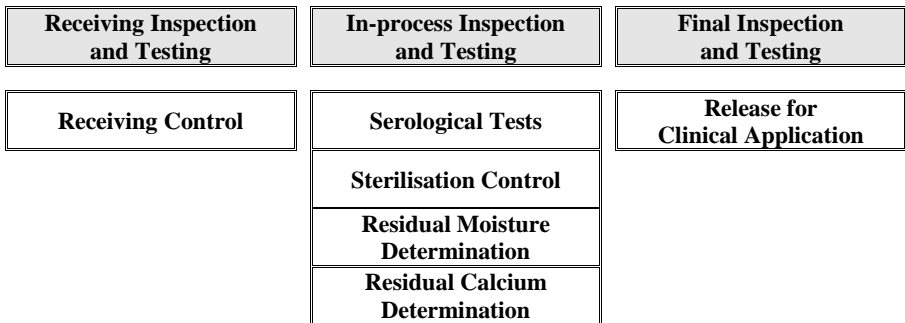


Fig. 6. Compliance between standard requirements and tissue banking practice concerning the quality assurance element “Inspection and Testing”.

2.11. Element 11: Control of inspection, measuring and test equipment

This element describes the requirement that all testing agents used in monitoring the stipulated quality requirements during the process must themselves be regularly monitored, calibrated and maintained.

In addition to many others, thermometers to monitor temperatures are for example test agents in tissue banking. A tissue bank should elaborate a test plan, in which all test agents and the rotation of monitoring and the responsibilities are recorded. Test agents which can no longer be used on account of unacceptable inaccuracies must be appropriately identified.

- Test agents: measuring instruments, testing equipment, test aids or gauges for checking test characteristics;
- Adjustment: minimisation of systematic measuring deviation through change in the test agent;
- Calibration: establishment of the systematic measuring deviation without change in the test agent.

In the DIZG, we only use test agents which have a sufficiently exact measurement range and a deviation of which in the measurement display lies within the inaccuracy allowed for this device. All test agents used are registered, identified and indicated whether they are in a correct condition. The use of the test agents takes place on the basis of the manufacturers' recommendations. For more complex measurement tasks, the member of staff assigned to the test is specially instructed and trained. This is documented in writing.

The measurement and testing equipment which must be calibrated is stipulated in a calibration plan. The calibration plan also contains the type of calibration and the form of documentation. If a test agent no longer conforms to its specifications, it is appropriately marked (quarantined) until a decision is made on its further use.

2.12. Element 12: Inspection and test status

This element describes the requirement that during a production process, the conformity or non-conformity of a product in regard to the quality inspections and testing carried out must be apparent at any time by means of an appropriate marking. Figure 7 shows the quarantine system for the production of allografts in the DIZG,

Quarantine 0	Receiving control not OK
Quarantine 1	Waiting for serological test results
Quarantine 2	Serological test OK, waiting for preparation
Quarantine 3	Preparation finished, waiting for sterilisation
Quarantine 4	Sterilisation OK, waiting for freeze-drying
Quarantine 5	Processing finished, waiting for sterile control
Storage	Sterile control OK, release for clinical application

Fig. 7. Quarantine system of DIZG: Example for the compliance between standard requirements and tissue banking practice for freeze-dried allografts concerning the quality assurance element "Inspection and Test Status".

showing the connection between process steps, represented as quarantine levels, following in-process inspection and, in the case of conformity, the transfer to the next process step (quarantine level). This element shows a close connection with elements 9 and 10.

2.13. Element 13: Control of non-conforming products

This element is directly connected with element 12. It describes how to deal with cells and tissue or the processed grafts for which non-conformity with the quality inspections exists. In this regard, it must be ensured that the faulty allografts do not end up back in processing by mistake.

The department heads of the DIZG have available to them, for every process or quarantine level, a catalogue of measures for deciding on the further use of the preparation, dependant on the result or identified fault, which extends up to the destruction of the product. In the cause of faults appearing for the first time, dependant on the type of fault, a consultation with the head of the department for quality control and the institute management takes place.

2.14. Element 14: Corrective and preventive action

The element describes how faults in the various stages of process management can be recorded and analysed. The process described here also ensures that appropriate measures will be taken in order to prevent their renewed appearance. In addition, regular clinic contacts (e.g. through transplantation protocols) are included in the catalogue of measures.

In the DIZG, the department heads are responsible for the acceptance of fault reports within the framework of process control. Fault analysis and conclusions for corrective action from complaints and preventative routine questions are discussed in a body consisting of department heads, production manager, head of quality control and management representative (Quality Management). Every staff member of the institute is obliged to report faults or events which occur, which he/she presumes to be faults, to the responsible department head. The systematic analysis of these reports is handled by the above-mentioned body.

Recognised faults can only be avoided in the future in so far as their causes are known, the corrective measures guaranteed and their effectiveness monitored. All faults are recorded in writing on the "Fault Report" form. The fault report contains:

- short description of the fault,
- type of fault,
- date of the fault report,
- description of the corrective action,
- naming of the person responsible,
- checking of the effectiveness of corrective action, and

all documents connected with the fault report or correction.

2.15. Element 15: Handling, storage, packaging, preservation and delivery

The core of this element is the description of how it is ensured that throughout the entire process run, the stipulated quality require-

ments are not negatively affected by processing, storage, packaging, preservation and delivery.

It describes the prerequisites, measures and control mechanisms which guarantee that consumable materials, biological parent materials (cells and tissue) used in the production of cell and tissue grafts and the finally processed grafts suffer no loss of quality during the above-mentioned processes.

The maintenance and control of the cold chain for allografts conserved with low temperatures, from the arrival of the tissue at the tissue bank until dispatch to the clinic can serve as an example from tissue banking. An additional increasingly more important example is the selection of suitable packaging (plastics, glass bottles, etc.). These must be *provably* suitable for the proposed purpose in accordance with national and international requirements. Certificates must be at hand to show that the packaging material is suitable, for example, for storage over a desired period (e.g. five years at room temperature) and for certain sterilisation processes (e.g. irradiation), that it is not permeable to bacteria, etc. Labelling and the provision of inserts also belong to this spectrum. These requirements are very precisely described in the Standards of EATB.

2.16. Element 16: Control of quality records

Quality records serve as evidence for the fulfilment of stipulated quality requirements and as evidence for the effectiveness of the QMS. In this element, the identification, collection, registration, accessibility, storage, safekeeping, care and elimination of quality records is described. This element is thus very closely connected to element 5.

The criteria for the testing of quality records are their correctness, formally and as regards content, their completeness, assignability and perfect legibility. These criteria are to be fulfilled first before the quality records are accepted as a component of the documentation.

The management representative bears the responsibility for the archiving and availability of the quality records.

2.17. Element 17: Internal quality audits

The QMS is periodically and spontaneously, that is to say without official announcement, tested for completeness, effectiveness and expedience through internal quality audits.

At the same time, the adherence to all quality system procedures, working instructions, standard operation procedures and inspection procedures is monitored. It is of decisive importance to register weak points, establish causes and introduce corrective action. In the carrying out of internal quality audits, there is special emphasis on documenting and, when necessary, improving the steady high system quality through self-monitoring in all areas of the DIZG.

The results of the internal audits must be recorded and evaluated in an audit report. As a result, corrective action must be taken should the audit reveal any shortcomings.

2.18. Element 18: Training

The standard assumes that a high quality standard can only be achieved with personnel who are adequately trained for the tasks and who have the necessary experience. For this reason, the further education requirement must be recorded and a training plan drawn up.

In addition, the DIZG demands from every employee the readiness for further training in their own responsibility and fixes this demand in the contract of employment.

2.19. Element 19: Servicing

The servicing element has in the true sense of the word no meaning for tissue banking. In an extended sense, professional co-operation with the clinical users can be understood. For example, surveys to record changes in clinical requirements or to receive satisfaction analyses would be suitable here. Information on new developments or tendencies in the specialist area could also be disseminated to the clinical users through, for example, the issuing of newsletters.

2.20. Element 20: Statistical techniques

Statistical techniques can be very useful for supplying information on correctly functioning processes. The standard always requires the use of statistical methods in areas where they can be sensibly utilised. Not just mathematical–statistical techniques in a narrow sense are meant in these cases. Surveys, market analyses and other methods are also included.

3. Reflections on the ISO 9000 Standard Series from the Point of View of Tissue Banking (Conclusions)

The construction of a QMS on the basis of the ISO 9000 standard series in tissue banking is still at its very beginning. Up to now, to the author's knowledge at the time of the drafting of this manuscript, there are two tissue banks in Europe and one in the United States which are certified. In Vietnam, one tissue bank works according to a national standard which practically corresponds to the ISO standard. In other branches of business, however, there are umpteen numbers which have experience with this standard extending back to the 1980s.

On the basis of our own experience, it can be said in summary that ISO 9000 is also well suited for the formation of the basis for implementing a QMS for tissue banking. The advantages of this standard series being very generally formulated, that is to say without any relation to a particular branch of business, and at the same time, exhibiting a high degree of complexity, speak for this recommendation.

In implementing a QMS in accordance with ISO 9000, the goal is normally, after the system comes into force, to bring evidence through an audit by an accredited certification body that the system is in conformity with the standard, is effective, fully established and finally, that the certificate is issued. On the other hand, this goal can only be achieved by means of a substantial personnel and financial expenditure. Therefore, there is the legitimate question as to whether for the reasons mentioned, the ISO 9000 standard series is appropriate