V.b. Annex I. Quality and risk management systems for human tissue products - Requirements

1 Scope

1.1 General

These requirements shall apply a quality management system and to a risk management system where an organization:

a) needs to demonstrate its ability to consistently provide human tissue product that meets customer and applicable regulatory requirements, and

b) aims to enhance customer satisfaction through the effective application of the system, including processes for continual improvement of the system and the assurance of conformity to customer and applicable regulatory requirements.

1.2 Application

1.2.1 The requirements specified in this annex are not intended to cover provisions related to other Directives regulating aspects of the process of manufacturing of HTPs, such as procurement and testing of cells and tissues.

1.2.2 The requirements specified in this annex have been prepared taking into consideration already published documents regulating Quality Systems for industrially manufactured healthcare products and are intended to cover all aspects of the Quality System. According to the characteristics of the product/process, some provisions may not be fully applicable because, in some instances, the production process cannot be fully standardized due to donor's variability.

1.2.3 The extent of the validation required to demonstrate of the process should be tailored to the development stage of the product. A full validation report should be available only when the HTP is ready for commercialization.

1.2.4 The requirements specified in this annex are intended to be applicable to all organizations, regardless of type, size and nature of human tissue product provided.
Where any requirement(s) cannot be applied due to the nature of an organization and its human tissue product, this can be considered for exclusion. Such exclusions and the supporting rationale shall be documented and shall not affect the organization's ability, or responsibility, to provide human tissue product that meets customer and applicable regulatory requirements.

2 Terms and definitions

Wherever the term "human tissue product" occurs, it can also mean "human tissue process", that is the process applied to obtain the human tissue product.

4 Quality management system

4.1 General requirements

The organization shall establish, document, implement and maintain quality and risk management systems and continually improve their effectiveness in accordance with the following requirements.

The organization shall:

a) identify the processes needed for the quality management system and their application throughout the organization (see 1.2);
b) determine the sequence and interaction of these processes;
c) determine criteria and methods needed to ensure that both the operation and control of these processes are effective;
d) ensure the availability of resources and information necessary to support the operation and monitoring of these processes;
e) monitor, measure and analyze these processes, and
f) implement actions necessary to achieve planned results and continual improvement of these processes.

These processes shall be managed by the organization in accordance with the requirements specified in this annex.

Where an organization chooses to outsource any process that affects human tissue product conformity with requirements, the organization shall ensure control over such processes. Control of such outsourced processes shall be identified within the quality management system.

NOTE. Processes needed for the quality management system referred to above should include processes for management activities, provision of resources, human tissue product realization and measurement.

4. 2 Documentation requirements

4.2.1 General

The quality management system documentation shall include

a) documented statements of a quality policy and quality objectives;
b) a quality manual;
c) a risk management file;
d) documented procedures as required by this annex;
e) documents needed by the organization to ensure the effective planning, operation and control of its processes; and
f) records as required in this annex (see 4.2.4).

NOTE 1. Where the term 'documented procedure" appears, this means that the procedure is established, documented, implemented and maintained.

NOTE 2. The extent of the quality management system documentation can differ from one organization to another due to

a) the size of organization and type of activities,
b) the complexity of processes and their interactions, and
c) the competence of personnel.

NOTE 3. The documentation can be in any form or type of medium.

4.2.2 Quality manual

The organization shall establish and maintain a quality manual that includes
a) the scope of the quality management system, including details of and justification for any exclusions (see 1.2);
b) the documented procedures established for the quality management system, or reference to them, and;
c) a description of the interaction between the processes of the quality management system.

4.2.3 Control of documents

Documents required by the quality management system shall be controlled. Records are a special type of document and shall be controlled according to the requirements given in 4.2.4.

A documented procedure shall be established to define the controls needed

a) to approve documents for adequacy prior to issue,
b) to review and update as necessary and re-approve documents,
c) to ensure that changes and the current revision status of documents are identified,
d) to ensure that relevant versions of applicable documents are available at points of use,
e) to ensure that documents remain legible and readily identifiable,
f) to ensure that documents of external origin are identified and their distribution controlled, and
g) to prevent the unintended use of obsolete documents, and to apply suitable identification to them if they are retained for any purpose,
h) to ensure that relevant changes are introduced only after any applicable regulatory approvals are obtained.

4.2.4 Control of records

Records shall be established and maintained to provide evidence of conformity to requirements and of the effective operation of the quality management system. Records shall remain legible, readily identifiable and retrievable. A documented procedure shall be established to define the controls needed for the identification, storage, protection, retrieval, retention time and disposition of records.
The time for record keeping shall be defined according to the requirements of applicable regulations.

5 Management responsibility

5.1 Management commitment

Top management shall provide evidence of its commitment to the development and implementation of the quality management system and continually improving its effectiveness by

a) communicating to the organization the importance of meeting customer as well as statutory and regulatory requirements;
b) establishing the quality policy;
c) ensuring that quality objectives are established;
d) conducting management reviews; and
e) ensuring the availability of resources.

For management responsibilities relating to risk management see 9.3.3.

5.2 Customer focus

Top management shall ensure that customer requirements are determined and are met with the aim of enhancing customer satisfaction (see 7.2.1 and 8.2.1).

5.3 Quality policy

Top management shall ensure that the quality policy:

a) is appropriate to the purpose of the organization;
b) includes a commitment to comply with requirements and continually improve the effectiveness of the quality management system;
c) provides a framework for establishing and reviewing quality objectives;
d) is communicated and understood within the organization; and
e) is reviewed for continuing suitability.

5.4 Planning

5.4.1 Quality objectives

Top management shall ensure that quality objectives, including those needed to meet requirements for human tissue product (see 7.1 a)), are established at relevant functions and levels within the organization. The quality objectives shall be measurable and consistent with the quality policy.

5.4.2 Quality management system planning

Top management shall ensure that

a) the planning of the quality management system is carried out in order to meet the requirements given in 4.1 and 5.1, as well as the quality objectives; and
b) the integrity of the quality management system is maintained when changes to the quality management system are planned and implemented.
c) ensure that a quality program is in place which covers adequate procedures for receiving, investigating, evaluating and documenting information received from other sources and for sharing with consignees and other establishments that are known to have recovered cells or tissue form the same donor any information pertaining to the integrity and function of a human cellular or tissue based product, possible contamination of the product or the potential transmission of communicable disease by the product.

5.5 Responsibility, authority and communication

5.5.1 Responsibility and authority

Top management shall ensure that responsibilities and authorities are defined and communicated within the organization.

5.5.2 Management representative

Top management shall appoint a member of management who, irrespective of other responsibilities, shall have responsibility and authority that includes

a) ensuring that processes needed for the quality management system are established, implemented and maintained;
b) reporting to top management on the performance of the quality management system and any need for improvement; and
c) ensuring the promotion of awareness of customer requirements throughout the organization.

NOTE. The responsibility of a management representative can include liaison with external parties on matters relating to the quality management system. The management representative shall report directly to the top management.

The designated person shall report to management on the performance of the quality program on no less than an annual basis. If this person also performs other tasks in the establishment, he or she shall not have final oversight over his or her own work

5.5.3 Internal communication

Top management shall ensure that appropriate communication processes are established within the organization and that communication takes place regarding the effectiveness of the quality management system.

5.6 Management review

5.6.1 General

Top management shall review the organization's quality management system, at planned intervals, to ensure its continuing suitability, adequacy and effectiveness. This review shall include assessing opportunities for improvement and the need for changes to the quality management system, including the quality policy and quality objectives. Records from management reviews shall be maintained (see 4.2.4).

5.6.2 Review input

The input to management review shall include information on

a) results of audits;
b) customer feedback;
c) process performance and product conformity;
d) status of preventive and corrective actions;
e) follow-up actions from previous management reviews;
f) changes that could affect the quality management system; and
g) recommendations for improvement.

5.6.3 Review output

The output from the management review shall include any decisions and actions related to

a) improvement of the effectiveness of the quality management system and its processes;
b) improvement of product and processes related to customer requirements; and
c) resource needs.

6 Resource management

6.1 Provision of resources

The organization shall determine and provide the resources needed
a) to implement and maintain the quality management system and continually improve its effectiveness; and
b) to enhance customer satisfaction by meeting customer requirements.

6.2 Human resources

6.2.1 General

Personnel performing work affecting product quality shall be competent on the basis of appropriate education, training, skills and experience.

6.2.2 Competence, awareness and training

The organization shall

a) determine the necessary competence for personnel performing work affecting human tissue product quality;
b) provide training or take other actions to satisfy these needs;
c) evaluate the effectiveness of the actions taken;
d) ensure that its personnel are aware of the relevance and importance of their activities and how they contribute to the achievement of the quality objectives; and
e) maintain appropriate records of education, training, skills and experience (see 4.2.4).

Specific training programs shall be instituted and implemented for production personnel. The training program shall include detailed instructions on the practices in place to ensure safety and effectiveness of the human tissue product and to protect the operators.

Only trained personnel shall be allowed to perform unattended operations.

6.3 Infrastructure

The organization shall determine, provide and maintain the infrastructure needed to achieve conformity to human tissue product requirements. Infrastructure includes, as applicable

a) buildings, workspace and associated utilities;
b) process equipment (both hardware and software); and
c) supporting services (such as transport or communication).

NOTE. For human tissue products, transport is a critical step and special care should be paid to it.

6.4 Work environment/facilities

The organization shall determine and manage the work environment needed to achieve conformity to human tissue product requirements.

6.4.1 The manufacture of human tissue products shall be carried out in clean areas entry to which should be through airlocks for personnel and/or for equipment and materials. Clean areas shall be maintained to an appropriate cleanliness standard and supplied with air which has passed through filters of an appropriate efficiency.

6.4.2 The various operations composing the production process, from reagent preparation to primary packaging, shall be carried out in appropriate areas within the clean area.

6.4.3 Each manufacturing operation shall require an appropriate environmental cleanliness level in the operational state in order to minimize the risks of particulate or microbial contamination of the product or materials being handled.

NOTE. This cleanliness is related to the type of process and of the containers (open or closed) used for cell culture. Use of closed, air-filtered containers is considered an effective containment system that may require less stringent cleanliness requirements for working environment, when supported by positive results of the validation tests.

6.4.4 In order to meet “in operation” conditions these areas shall be designed to reach certain specified air-cleanliness levels in the “at rest” occupancy state.

NOTE 1. The “at-rest” state is the condition where the installation is installed and operating, complete with production equipment but with no operating personnel present. The “in operation” state is the condition where the installation is functioning in the defined operating mode with the specified number of personnel working.

The “in operation” and “at rest” states shall be defined for each clean room or suite of clean rooms.

NOTE 2. For the manufacture of human tissue products 4 grades can be distinguished.

Grade A: The local zone for high risk operations, i.e. when cells and/or tissues are exposed unprotected to the environment. Normally such conditions are provided by a laminar air flow work station. Laminar air flow systems should provide a homogeneous air speed in a range of 0.36 – 0.54 m/s (guidance value) at the working position in open clean room applications.

For this Grade, the maintenance of laminarity has to be demonstrated and validated.

Suitable alternatives to laminar air flow systems are closed isolators and glove boxes.
Grade B: This is the background environment for the grade A zone when open containers are used for cell containment.

Grade C: This is the background environment for the grade A zone when closed containers are used for cell containment or when the human tissue product is terminally sterilized.

Grade D: Clean areas for carrying out less critical stages in the manufacture of sterile products.

6.4.5 Where aseptic operations are performed, monitoring shall be adequate for the length of the process and shall be performed using methods such as settle plates, volumetric air and surface sampling (e.g. swabs and contact plates). Sampling methods used in operation shall not interfere with zone protection. Available results from monitoring shall be considered when reviewing batch documentation for finished product release. Surfaces and personnel shall be monitored after critical operations.

6.4.6 Only the minimum number of personnel required shall be present in clean areas; this is particularly important during aseptic processing. Inspections and controls shall be conducted outside the clean areas as far as possible.

6.4.7 Changing and washing shall follow a written procedure designed to minimize contamination of clean area clothing or carry-through of contaminants to the clean areas.

6.4.8 Wristwatches, make-up and jewellery shall not be worn in clean areas.

6.4.9 The immunological status of personnel shall be taken into consideration for product safety. All personnel engaged in production, maintenance, testing and animal care (and inspectors) shall be vaccinated where necessary with appropriate specific vaccines and have regular health checks.

NOTE. Apart from the obvious problem of exposure of staff to infectious agents it is necessary to avoid the risk of contamination of a production batch with infectious agents.

Any changes in the immunological status of personnel which could adversely affect the quality of the product shall preclude work in the production area.

6.4.10 Visitors shall generally be excluded from production areas.

6.4.11 The clothing and its quality shall be appropriate for the process and the grade of the working area. It shall be worn in such a way as to protect the product from contamination:

For Grade C, hair and, where relevant, beard and moustache shall be covered. A single or two-piece trouser suit, gathered at the wrists and with high neck and appropriate shoes or overshoes shall be worn that shed virtually no fibres nor particulate matter.

For Grades A/B, headgear shall totally enclose hair and, where relevant, beard and moustache; it shall be tucked into the neck of the suit; a face mask shall be worn to prevent the shedding of droplets. Appropriate sterilized, non-powdered rubber or plastic gloves and sterilized or disinfected footwear shall be worn. Trouser-legs shall be tucked inside the footwear and garment sleeves into the gloves. The protective clothing shall shed virtually no fibres nor particulate matter and retain particles shed by the body.

These requirements are applied to personnel working inside areas classified as Grade A or B. Operations performed in laminar flow hoods, isolators or glove boxes shall follow the requirements applicable to the body part that is inside the work station.

6.4.12 Special attention shall be paid to cross-contamination of cross-infection when cells or tissues from multiple donors are handled in the same working area.

6.4.13 Where negative pressure areas or safety cabinets are used for aseptic processing of cells and tissues, they shall be surrounded by a positive pressure containment zone.

6.4.14 The layout and design of production areas and equipment shall permit effective cleaning and decontamination (e.g. by fumigation). The adequacy of cleaning and decontamination procedures shall be validated.

6.4.15 Equipment used during handling of live organisms shall be designed to maintain cultures in a pure state and uncontaminated by external sources during processing.

6.4.16 Changing rooms shall be designed as airlocks and used to provide physical separation of the different stages of changing and so minimize microbial and particulate contamination of protective clothing. They shall be flushed effectively with filtered air.

6.4.17 A warning system shall be provided to indicate failure in the air supply. Indicators of pressure differences shall be fitted between areas where these differences are important.

NOTE. The facility should have an appropriate size and divided in separate areas, or other control systems should be in place to prevent contamination, cross-contamination, improper labeling, accidental exposure of human cellular and tissue based products to communicable disease

6.4.18 Procedures for facility cleaning shall be in place, cleaning and sanitation activities shall be documented and recorded

6.5 Environmental control and monitoring

Procedures shall be in place where environment could reasonably have an effect on the function and integrity of human cellular and tissue based products or cause contamination. Procedures shall, provide, where appropriate monitoring systems for temperature, humidity, ventilation, air filtration, cleaning and disinfecting rooms to ensure aseptic processing, monitoring for orgasm. Each system shall be periodically be inspected. Records shall be maintained.

6.6 Storage

Each establishment shall control its storage areas and stock rooms to prevent mix--ups, commingling, deterioration, contamination and cross contamination. Storage temperature shall be maintained. Expiration date shall be assigned (where applicable) to each product

7 Human tissue product realization

7.1 Planning of human tissue product realization

The organization shall plan and develop the processes needed for human tissue product realization. Planning of human tissue product realization shall be consistent with the requirements of the other processes of the quality management system (see 4.1).

In planning human tissue product realization, the organization shall determine the following, as appropriate:

a) quality objectives and requirements for the human tissue product;
b) requirements for the equipment, environments and facilities;
c) the need to establish processes, documents, and provide resources specific to the human tissue product;
d) required verification, validation, monitoring, inspection and test activities specific to the human tissue product and the criteria for human tissue product acceptance;
e) records needed to provide evidence that the realization processes and resulting human tissue product meet requirements (see 4.2.4).

The output of this planning shall be in a form suitable for the organization's method of operations.

NOTE 1. A document specifying the processes of the quality management system (including the human tissue product realization processes) and the resources to be applied to a specific human tissue product, project or contract, can be referred to as a quality plan.

NOTE 2. The organization may also apply the requirements given in 7.3 to the development of human tissue product realization processes.

7.2 Customer-related processes

7.2.1 Determination of requirements related to the product

The organization shall determine

a) requirements specified by the customer, including the requirements for delivery and post-delivery activities;
b) requirements not stated by the customer but necessary for specified or intended use, where known;
c) statutory and regulatory requirements related to the human tissue product; and
d) any additional requirements determined by the organization.

7.2.2 Review of requirements related to the human tissue product

The organization shall review the requirements related to the human tissue product. This review shall be conducted prior to the organization's commitment to supply a product to the customer (e.g. submission of tenders, acceptance of contracts or orders, acceptance of changes to contracts or orders) and shall ensure that

a) human tissue product requirements are defined and comply with applicable regulation;
b) contractor order requirements differing from those previously expressed are resolved; and
c) the organization has the ability to meet the defined requirements.

Records of the results of the review and actions arising from the review shall be maintained (see 4.2.4).

Where the customer provides no documented statement of requirement, the customer requirements shall be confirmed by the organization before acceptance.

Where human tissue product requirements are changed, the organization shall ensure that relevant documents are amended and that relevant personnel are made aware of the changed requirements.

NOTE. In some situations, a formal review is impractical for each order. Instead the review can cover relevant human tissue product information.

7.2.3 Customer communication

The organization shall determine and implement effective arrangements for communicating with customers in relation to

a) human tissue product information;
b) enquiries, contracts or order handling, including amendments; and
c) customer feedback, including customer complaints.

7.3 Design and development

7.3.1 Design and development planning

The organization shall plan and control the design and development of human tissue product.

During the design and development planning, the organization shall determine

a) the design and development stages;
b) the risk management procedures (see xx.yy), review, verification and validation that are appropriate to each design and development stage; and

c) the responsibilities and authorities for design and development.

The organization shall manage the interfaces between different groups involved in risk management, and in design and development to ensure effective communication and clear assignment of responsibility.

Planning output shall be updated, as appropriate, as the design and development progresses.

7.3.2 Design and development inputs

Inputs relating to product requirements shall be determined and records maintained (see 4.2.4). These inputs shall include

a) functional and effectiveness requirements;
b) the results of risk management;
c) applicable statutory and regulatory requirements;
d) where applicable, information derived from previous similar human tissue products; and
e) other requirements essential for design and development.

These inputs shall be reviewed for adequacy. Requirements shall be complete, unambiguous and not in conflict with each other.

7.3.3 Design and development outputs

The outputs of design and development shall be provided in a form that enables verification against the design and development input and shall be approved prior to release.

Design and development outputs shall

a) meet the input requirements for design and development;
b) provide appropriate information for purchasing, production and for service provision;
c) contain or reference human tissue product acceptance criteria;
d) specify the characteristics of the human tissue product that are essential for its safe and proper use;
e) define validation plans

7.3.4 Design and development review

At suitable stages, systematic reviews of design and development shall be performed in accordance with planned arrangements (see 7.3.1)

a) to evaluate the ability of the results of design and development to meet requirements; and
b) to identify any problems and propose necessary actions.

Participants in such reviews shall include representatives of functions concerned with the design and development stage(s) being reviewed. Records of the results of the reviews and any necessary actions shall be maintained (see 4.2.4).

7.3.5 Design and development verification

Verification shall be performed in accordance with planned arrangements (see 7.3.1) to ensure that the design and development outputs have met the design and development input requirements. Records of the results of the verification and any necessary actions shall be maintained (see 4.2.4).

7.3.6 Design and development validation

Design and development validation shall be performed in accordance with planned arrangements (see 7.3.1) to ensure that the resulting human tissue product is capable of meeting the requirements for the specified application or intended use, where known. Records of the results of validation and any necessary actions shall be maintained (see 4.2.4).

7.3.7 Control of design and development changes

Design and development changes shall be identified and records maintained. The changes shall be reviewed, verified and validated, as appropriate, and approved before implementation. The review of design and development changes shall include evaluation of the effect of the changes on constituent parts and on human tissue product already delivered.
Changes made on human tissue products already in the clinical investigation stage shall be assessed taking into account the impact of the changes on the trial. The assessment shall be documented.
Records of the results of the review of changes and any necessary actions shall be maintained (see 4.2.4).

7.4 Materials utilized in human tissue products

NOTE. The provisions of this section apply to materials, reagents, equipment and services that may affect the quality of the Human Tissue Product.

The definition of starting material does not include donor cells or tissue, for which a specific Directive applies.
7.4.1 Supply process

The organization shall ensure that any starting material used for the production of human tissue product conforms to specified requirements and/or regulatory provisions. The type and extent of control applied to the supplier and the supplied material shall be dependent upon the effect of that material upon subsequent human tissue product realization or the final human tissue product.

The organization shall evaluate and select suppliers based on their ability to supply the necessary material(s) in accordance with the organization's requirements. Criteria for selection, evaluation and re-evaluation shall be established. Records of the results of evaluations and any necessary actions arising from the evaluation shall be maintained (see 4.2.4).

Note : Supplies and reagents shall be verified to meet specifications designed to prevent circumstances that increase the risk of the introduction, transmission, or spread of communicable disease through product contamination or the impairment of product function or integrity and shall not be used until such verification is completed. Reagents shall be sterile of appropriate grade for the intended use. Procedures for production of in house reagents shall be validated or verified. Records for the use of each supply or reagents, which shall include the identification of each human cellular or tissue based product manufactured with the supply, reagent

7.4.2 Supply information

Supply information shall describe the material to be procured, including where appropriate

a) requirements for approval of material, procedures, processes and equipment;
b) requirements for qualification of personnel; and
c) quality management system requirements.

The organization shall ensure the adequacy of specified supply requirements prior to their communication to the supplier.

Procedures shall be in place for the following activities, receipt, acceptance, rejection, distribution and destruction

7.4.3 Verification of supplied product, receipt and distribution

The organization shall establish and implement the inspection or other activities necessary for ensuring that supplied material meets specified supply requirements.

Where the organization intends to perform verification at the supplier's premises, the organization shall state the intended verification arrangements and method of material release in the supply information.

The status of the incoming product shall be determined and identified promptly after receipt. Product shall be inspected according to procedures for damage, contamination, deterioration. Release criteria shall be in place designed to prevent release of products that are in quarantine or contaminated. Packaging shall be designed and validated to ensure product function and integrity. Shipping conditions shall be defined where appropriate. Procedures shall be in place for return to inventory.

7.5 Production and service provision

7.5.1 Control of production and service provision

7.5.1.1 The organization shall plan and carry out production and service provision under controlled conditions. Controlled conditions shall include, as applicable

a) the availability of information that describes the characteristics of the human tissue product;
b) the availability of work instructions, as necessary;
c) the use of suitable equipment;
d) the availability and use of monitoring and measuring devices;
e) the implementation of monitoring and measurement; and
f) the implementation of release, delivery and post-delivery activities.

7.5.1.2 Precautions to minimize contamination shall be taken during all processing stages including the stages before sterilization.

7.5.1.3 Water sources, water treatment equipment and treated water shall be monitored regularly for chemical and biological contamination and, as appropriate, for endotoxins. Records shall be maintained of the results of the monitoring and of any action taken.

7.5.1.4 Activities in clean areas and especially when aseptic operations are in progress shall be kept to a minimum and movement of personnel shall be controlled and methodical, to avoid excessive shedding of particles and organisms due to over-vigorous activity. The ambient temperature and humidity shall not be uncomfortably high because of the nature of the garments worn.

7.5.1.5 Containers and materials liable to generate fibres shall be minimized in clean areas.

7.5.1.6 Components, containers and equipment shall be handled after the final cleaning process in such a way that they are not re-contaminated. Disposable materials shall be used whenever possible or practical.

7.5.1.7 The time between the start of the preparation of a solution and its sterilization or filtration through a micro-organism-retaining filter shall be minimized. There shall be a set maximum permissible time for each product that takes into account its composition and the prescribed method of storage.

7.5.1.8 The efficacy of any new procedure shall be validated, and the validation verified at scheduled intervals based on performance history or when any significant change is made in the process or equipment.

7.5.1.9 When equipment maintenance has been carried out within the clean area, the area shall be cleaned, disinfected and/or sterilized where appropriate, before processing recommences if the required standards of cleanliness and/or asepsis have not been maintained during the work.

7.5.1.10 Water treatment plants and distribution systems shall be designed, constructed and maintained so as to ensure a reliable source of water of an appropriate quality. They shall not be operated beyond their designed capacity.

7.5.1.11 All equipment such as sterilizers used in the preparation of human tissue products, air handling and filtration systems, air vent and gas filters, water treatment, generation, storage and distribution systems shall be subject to validation and planned maintenance.

7.5.1.12 The sanitation of clean areas is particularly important and they shall be cleaned thoroughly in accordance with a written program. Where disinfectants are used, more than one type should be employed.

Monitoring shall be undertaken regularly in order to detect the development of resistant strains.

Disinfectants and detergents shall be monitored for microbial contamination; dilutions shall be kept in previously cleaned containers and shall only be stored for defined periods unless sterilized.

NOTE. Fumigation of clean areas may be useful for reducing microbiological contamination in inaccessible places.

7.5.1.13 In-process controls play a specially important role in ensuring the consistency of the quality of human tissue products and those controls, which are crucial for quality but which cannot be carried out on the finished product, shall be performed at an appropriate stage of production.

NOTE. Special procedures need to be in designed to prevent circumstances that increase the risk of the introduction, transmission and spread of communicable disease through the use of human cellular and tissue based products by ensuring that the products do not contain relevant communicable disease agents; that the products do not become contaminated during manufacturing and that function and integrity of the products are not impaired through improper manufacturing.

Such procedures need to be reviewed every 12 months

7.5.1.14 Human cells or tissue from two or more donors shall not be pooled (placed in physical contact or mixed in a single receptacle) during manufacturing

7.5.2 Validation of processes for production and service provision

7.5.2.1 The organization shall validate any processes for production and service provision where the resulting output cannot be verified by subsequent monitoring or measurement. This includes any processes where deficiencies become apparent only after the human tissue product is in use or the service has been delivered.

Validation shall demonstrate the ability of these processes to achieve planned results.

The organization shall establish arrangements for these processes including, as applicable

a) defined criteria for review and approval of the processes,
b) approval of equipment and qualification of personnel,
c) use of specific methods and procedures,
d) requirements for records (see 4.2.4), and
e) revalidation.

Risk management shall demonstrate analysis of potential hazards with respect to safety and identify need for validation. This shall demonstrate how to prevent and reduce the risk of contamination by adventitious agents such as viruses, bacteria, fungi and TSE-associated prions during the processing. Validation shall demonstrate that the procedure and process is effective. Procedures shall be in place to prevent contamination during the processing

7.5.2.2 Validation of aseptic processing shall include a process simulation test in which all operations are made without donor cells and/or tissues. If reagents contain antibiotics, they shall be absent in the simulation test.

Process simulation tests shall be performed as initial validation with three consecutive satisfactory simulation tests per shift and repeated at defined intervals and after any significant modification to the HVAC-system, equipment, process and number of shifts.

Normally process simulation test shall be repeated once a year per process. The number of containers used for media fills shall be sufficient to enable a valid evaluation. The manufacturer shall establish alert and action limits. Any contamination shall be investigated.

7.5.2.3 Care shall be taken that any validation does not compromise the processes

7.5.2.4 If computers or automated data processing systems are used as part of the quality program, as part of manufacture or tracking, or for maintaining data or records related to the manufacture or tracking of human

cellular or tissue based products, the establishment shall validate computer software for its intended use according to an established protocol.

Any process- related claims in labeling or promotional materials for human cellular or tissue based products, e.g. claims for sterility or viral inactivation shall be based on a validated procedure. When changes or deviations occur, the establishment shall fully investigate on the causes and on the impact that they have on the risk management

7.5.3 Identification and traceability

The organization shall identify the human product by suitable means throughout human tissue product realization.

The organization shall identity the human tissue product status with respect to monitoring and measurement requirements.

Where traceability is a requirement, the organization shall control and record the unique identification of the human tissue product (see 4.2.4).

Procedures shall be in place to control labeling of human cellular and tissue based products to ensure proper product identification and to prevent mix-up.

Each establishment shall establish and maintain a method for product tracking that enables the tracking of all human tissue products. Distinct identification code system shall be in place.

7.5.4 Customer property

The organization shall exercise care with customer property while it is under the organization's control or being used by the organization. The organization shall identify, verify, protect and safeguard customer property provided for use or incorporation into the human tissue product. If any customer property is lost, damaged or otherwise found to be unsuitable for use, this shall be reported to the customer and records maintained (see 4.2.4).

NOTE. Customer property can include intellectual property

7.5.5 Preservation of human tissue product

The organization shall preserve the conformity of human tissue product during internal processing and delivery to the intended destination. This preservation shall include identification, handling, packaging, storage and protection. Preservation shall also apply to the constituent parts of a human tissue product.
The manufacturer shall be allowed to retain a proper amount of retention samples to conduct any investigation should be necessary after delivery of the human tissue product

7.6 Control of monitoring and measuring devices

The organization shall determine the monitoring and measurement to be undertaken and the monitoring and measuring devices needed to provide evidence of conformity of human tissue product to determined requirements (see 7.2.1).

The organization shall establish processes to ensure that monitoring and measurement can be carried out and are carried out in a manner that is consistent with the monitoring and measurement requirements.

Where necessary to ensure valid results, measuring equipment shall

a) be calibrated or verified at specified intervals, or prior to use, against measurement standards traceable to international or national measurement standards; where no such standards exist, the basis used for calibration or verification shall be recorded;
b) be adjusted or re-adjusted as necessary;
c) be identified to enable the calibration status to be determined;
d) be safeguarded from adjustments that would invalidate the measurement result;
e) be protected from damage and deterioration during handling, maintenance and storage.

In addition, the organization shall assess and record the validity of the previous measuring results when the equipment is found not to conform to requirements. The organization shall take appropriate action on the equipment and any human tissue product affected. Records of the results of calibration and verification shall be maintained (see 4.2.4).

When used in the monitoring and measurement of specified requirements, the ability of computer software to satisfy the intended application shall be confirmed. This shall be undertaken prior to initial use and reconfirmed as necessary.

8 Measurement, analysis and improvement

8.1 General

The organization shall plan and implement the monitoring, measurement, analysis and improvement processes needed

a) to demonstrate conformity of the human tissue product,
b) to ensure conformity of the quality management system; and
c) to continually improve the effectiveness of the quality management system.

This shall include determination of applicable methods, including statistical techniques, and the extent of their use.

8.2 Monitoring and measurement

8.2.1 Customer satisfaction

As one of the measurements of the performance of the quality management system, the organization shall monitor information relating to customer perception as to whether the organization has met customer requirements. The methods for obtaining and using this information shall be determined.

8.2.2 Internal audit

The organization shall conduct internal audits at planned intervals to determine whether the quality management system

a) conforms to the planned arrangements (see 7.1), to the requirements of this annex and to the quality management system requirements established by the organization; and
b) is effectively implemented and maintained.

An audit program shall be planned, taking into consideration the status and importance of the processes and areas to be audited, as well as the results of previous audits. The audit criteria, scope, frequency and methods shall be defined. Selection of auditors and conduct of audits shall ensure objectivity and impartiality of the audit process. Auditors shall not audit their own work.

The responsibilities and requirements for planning and conducting audits, and for reporting results and maintaining records (see 4.2.4) shall be defined in a documented procedure.

The management responsible for the area being audited shall ensure that actions are taken without undue delay to eliminate detected nonconformities and their causes. Follow-up activities shall include the verification of the actions taken and the reporting of verification results (see 8.5.2).

Quality audits shall be performed at least annually by individuals with sufficient knowledge , training and experience to identify problems in the specific processes under review.

8.2.3 Monitoring and measurement of processes

The organization shall apply suitable methods for monitoring and, where applicable, measurement of the quality management system processes. These methods shall demonstrate the ability of the processes to achieve planned results. When planned results are not achieved, correction and corrective action shall be taken, as appropriate, to ensure conformity of the human tissue product.

8.2.4 Monitoring and measurement of product

The organization shall monitor and measure the characteristics of the product to verify that product requirements have been met. This shall be carried out at appropriate stages of the human tissue product realization process in accordance with the planned arrangements (see 7.1).

Evidence of conformity with the acceptance criteria shall be maintained. Records shall indicate the person(s) authorizing release of human tissue product (see 4.2.4).

Human tissue product release and service delivery shall not proceed until the planned arrangements (see 7.1) have been satisfactorily completed, unless otherwise approved by a relevant authority and, where applicable, by the customer.

Procedures shall be in place for making changes to the process. Any such change shall be verified or validated to ensure that the change does not create an adverse impact elsewhere in the operation and shall be approved before implementation. All changes shall be documented

8.3 Control of nonconforming human tissue product

The organization shall ensure that human tissue product which does not conform to the specified requirements requirements is identified and controlled to prevent its unintended use or delivery. The controls and related responsibilities and authorities for dealing with nonconforming human tissue product shall be defined in a documented procedure.

The organization shall deal with nonconforming human product by one or more of the following ways:

a) by taking action to eliminate the detected nonconformity;
b) by authorizing its use, release or acceptance under concession by a relevant authority and, where applicable, by the customer;
c) by taking action to preclude its original intended use or application.

Records of the nature of nonconformities and any subsequent actions taken, including concessions obtained, shall be maintained (see 4.2.4).

When nonconforming human tissue product is corrected it shall be subject to re-verification to demonstrate conformity to the requirements.

When nonconforming human product is detected after delivery or use has started, the organization shall take action appropriate to the effects, or potential effects, of the nonconformity.

8.4 Analysis of data

The organization shall determine, collect and analyze appropriate data to demonstrate the suitability and effectiveness of the quality management system and to evaluate where continual improvement of the effectiveness of the quality management system can be made. This shall include data generated as a result of monitoring and measurement and from other relevant sources.

The analysis of data shall provide information relating to

a) customer satisfaction (see 8.2.1);
b) conformity to human tissue product requirements (see 7.2.1);
c) characteristics and trends of processes and products including opportunities for preventive action; and
d) suppliers.

8.5 Improvement

8.5.1 Continual improvement

The organization shall continually improve the effectiveness of the quality management and risk management systems through the use of the quality and risk management policies, quality and risk management objectives, audit results, analysis of data, corrective and preventive actions and management review.

8.5.2 Corrective action

The organization shall take action to eliminate the cause of nonconformities in order to prevent recurrence. Corrective actions shall be appropriate to the effects of the nonconformities encountered.

A documented procedure shall be established to define requirements for

a) reviewing nonconformities (including customer complaints);

b) determining the causes of nonconformities;
c) evaluating the need for action to ensure that nonconformities do not recur;
d) determining and implementing action needed;
e) records of the results of action taken (see 4.2.4); and
f) reviewing corrective action taken.

Documentation of corrective action shall include where appropriate:

1) the identification of the human cellular or tissue based product affected and a description of disposition
2) the nature of the problem requiring corrective action
3) dates of the corrective action
4) investigating and documenting all product deviations
5) ensuring proper training and education of personnel

8.5.3 Preventive action

The organization shall determine action to eliminate the causes of potential nonconformities in order to prevent their occurrence. Preventive actions shall be appropriate to the effects of the potential problems.

A documented procedure shall be established to define requirements for

a) determining potential nonconformities and their causes;
b) evaluating the need for action to prevent occurrence of nonconformities;
c) determining and implementing action needed;
d) records of results of action taken (see 4.2.4); and
e) reviewing preventive action taken.

Each establishment shall perform a periodic review and analyses of all product deviations ate least once per year, for the purpose of trends, and adopting appropriate preventive measures.

9 Specific requirements for the risk management of human tissue products

9.1 General

Clause 9 of this annex specifies a procedure for the organization to identify the hazards associated with human tissue products, estimate and evaluate the risks, control these risks and monitor the effectiveness of the control. The requirements of this standard are applicable to all stages of the life cycle of a human tissue product.

The requirements in clause 9 do not apply to clinical judgements relating to the use of a human tissue product nor do they specify acceptable levels of risk.

9.2 Term(s) and definition(s)

9.2.1

accompanying document: document accompanying a human tissue product and containing important information for the medical professional and patient regarding safety

9.2.2

harm: physical injury or damage to the health of people, or damage to property or the environment

9.2.3

hazard: potential source of harm

9.2.4

hazardous situation: circumstance in which people, property or the environment are exposed to one or more hazard(s)

9.2.5

intended use/intended purpose: use of a human tissue product, a process or a service in accordance with the specifications, instructions and information provided by the organization

9.2.6

organization: natural or legal entity with responsibility for the design, manufacture, packaging or labelling of a human tissue product or adapting a human tissue product before it is placed on the market and/or put into service, regardless of whether these operations are carried out by that person himself or on his behalf by a third party.

9.2.7

objective evidence: information which can be proven true, based on facts obtained through observation, measurement, test or other means

9.2.8

procedure: specific way to perform an activity

9.2.10

process: set of inter-related resources and activities which transform inputs into outputs

9.2.11

record: document which furnishes objective evidence of activities performed or results achieved

9.2.12

residual risk: risk remaining after protective measures have been taken

9.2.13

risk: combination of the probability of occurrence of harm and the severity of that harm

9.2.14

risk analysis: systematic use of available information to identify hazards and to estimate their risk

9.2.15

risk assessment: overall process comprising a risk analysis and a risk evaluation

9.2.16

risk control: process through which decisions are reached and protective measures are implemented for reducing risks to, or maintaining risks within, specified levels

9.2.17

risk evaluation: judgement, on the basis of risk analysis, of whether a risk which is acceptable has been achieved in a given context based on the current values of society

9.2.18

risk management: systematic application of management policies, procedures and practices to the tasks of analyzing, evaluating and controlling risk

9.2.19

risk management file: set of records and other documents, not necessarily contiguous, that are produced by a risk management process

9.2.20

safety: freedom from unacceptable risk

9.2.21

severity: measure of the possible consequences of a hazard

9.2.22

verification: confirmation by examination and provision of objective evidence that specified requirements have been fulfilled

NOTE. In design and development, verification concerns the process of examining the result of a given activity to determine conformity with the stated requirement for that activity.

General requirements for risk management of human tissue products

9.3.1 Regulatory requirements

Due to the wide variety of human tissue products covered by this Regulation, subclause 9.3.3 shall apply as appropriate.

9.3.2 Risk management process

The organization shall establish and maintain a process for identifying hazards associated with a human tissue product, estimating and evaluating the associated risks, controlling these risks and monitoring the effectiveness of the control. This process shall be documented and shall include the following elements:

- risk analysis;
- risk evaluation;
- risk control; and
- post-production information.

Where a documented product design/development process exists, it shall incorporate the appropriate parts of the risk management process.

NOTE 1. A documented product design/development process can be used to deal with safety in a systematic manner, and in particular to enable the early identification of hazards in complex systems and environments.

NOTE 2. A schematic representation of the risk management process is shown in Figure 1.

9.3.3 Management responsibilities

The organization shall:

a) define its policy for determining acceptable risk.

b) ensure the provision of adequate resources;

c) ensure the assignment of trained personnel (see 0) for management, performance of work and assessment activities;

d) review the results of risk management activities at defined intervals to ensure continuing suitability and effectiveness of the risk management process.

The above shall be documented in the risk management file.

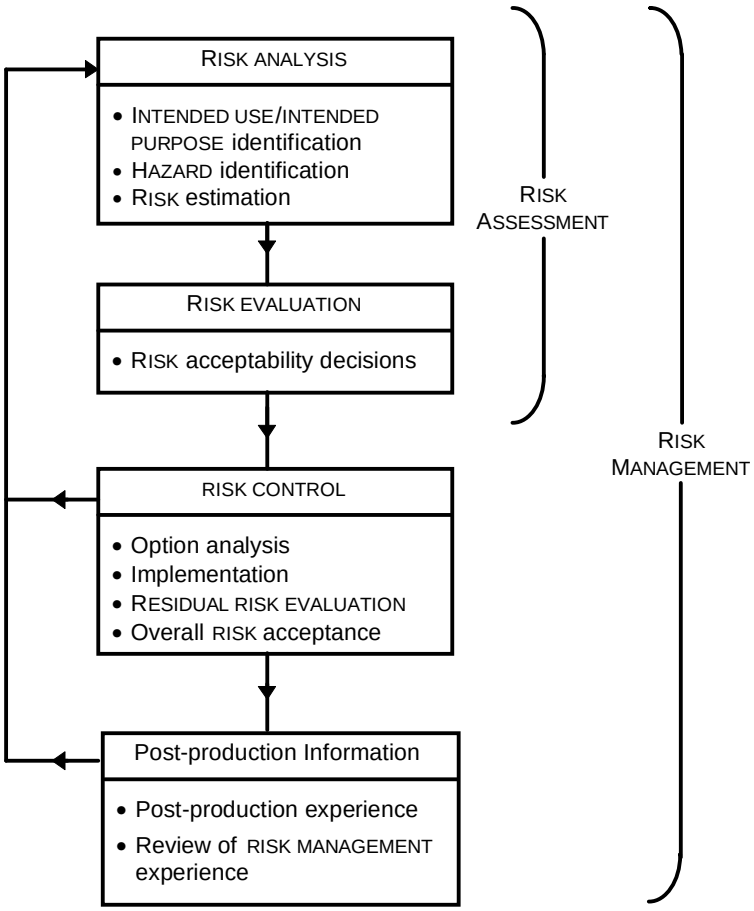

Figure 1 - Schematic representation of the risk management process

9.3.4 Qualification of personnel

The organization shall ensure that those performing risk management tasks include persons with knowledge and experience appropriate to the tasks assigned to them. This shall include, where appropriate, knowledge and experience of the human tissue product and its use and risk management techniques. Record of appropriate qualification shall be maintained.

9.3.5 Risk management plan

For the particular human tissue product being considered, the organization shall prepare a risk management plan in accordance with the risk management process. The risk management plan shall be part of the risk management file.

This plan shall include the following:

a) scope of the plan, identifying and describing the human tissue product and the life cycle phases for which the plan is applicable;

b) a verification plan;

c) allocation of responsibilities;

d) requirements for review of risk management activities; and

e) criteria for risk acceptability.

NOTE The criteria for risk acceptability will do much to determine the ultimate effectiveness of the risk management process. Refer to Annex zzz for guidance on establishing such criteria.

If the plan changes during the life cycle of the human tissue product, a record of the changes shall be maintained in the risk management file.

9.3.6 Risk management file

For the particular human tissue product being considered, the results of all risk management activities shall be recorded and maintained in the risk management file.

NOTE 1. The records and other documents that make up the risk management file may form part of other documents and files required.

NOTE 2. The risk management file need not physically contain all the documents required by this annex. However, it should contain at least references or pointers to all required documentation. The organization should be able to assemble the information referenced in the risk management file in a timely fashion.

9.4 Risk analysis

9.4.1 Risk analysis procedure

A risk analysis, as described in 9.4.2 to 9.9.4.4, shall be performed and the conduct and results of the risk analysis shall be recorded in the risk management file.

NOTE. If a risk analysis is available for a similar human tissue product, it may be used as a reference provided it can be demonstrated that the processes are similar or that the changes that have

been made will not introduce significant differences in results. This should be based on a systematic evaluation of the changes and the ways they can influence the various hazards present.

In addition to the records required in 9.4.2 to 9.9.4.4, the documentation of the conduct and results of the risk analysis shall include at least the following:

a) a description and identification of the human tissue product or accessory that was analyzed;

b) identification of the person(s) and organization which carried out the risk analysis;

c) the date of the analysis.

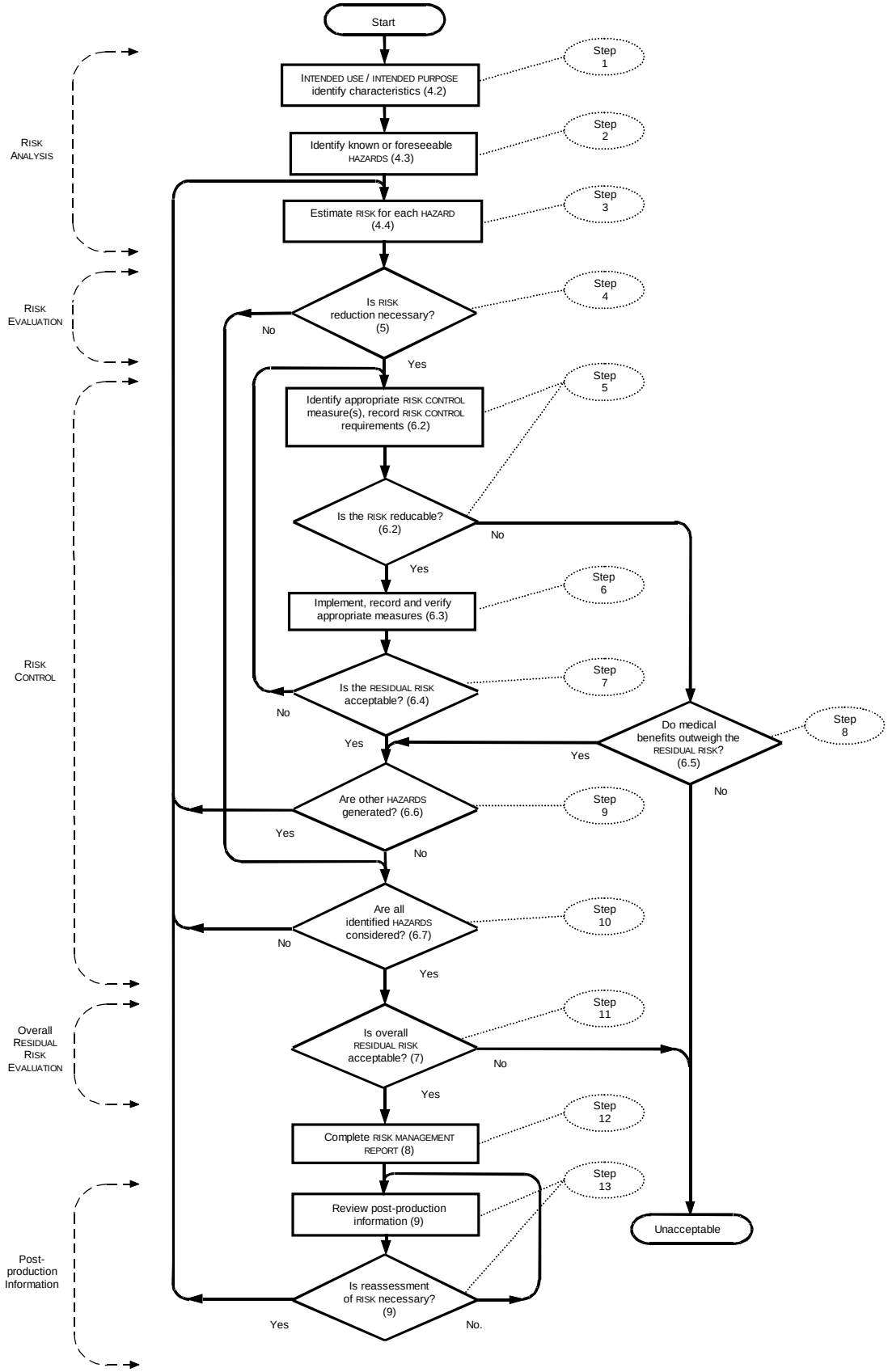

Figure 2 — Overview of risk management activities as applied to human tissue products

9.4.2 Intended use/intended purpose and identification of characteristics related to the safety of human tissue products (Step 1)

For the particular human tissue product being considered, the organization shall describe the intended use/intended purpose and any reasonably foreseeable misuse. The organization shall list all those qualitative and quantitative characteristics that could affect the safety of the human tissue product, and, where appropriate, their defined limits (see Note 1). These records shall be maintained in the risk management file.

9.4.3 Identification of known or foreseeable hazards (Step 2)

The organization shall compile a list of known or foreseeable hazards associated with the human tissue product. Previously recognized hazards shall be identified. This list shall be maintained in the risk management file.

Foreseeable sequences of events which may result in a hazardous situation shall be considered and recorded.

NOTE 1. Examples of possible hazards related to human tissue products are listed in Annex xz as an aide-memoire. These are illustrative examples only and should not be considered as a definitive list for any given human tissue product..

NOTE 2. To identify hazards not previously recognized, systematic methods appropriate to the specific situation may be used

.

9.4.4 Estimation of the risks for each hazard (Step 3)

For each identified hazard, the risks shall be estimated using available information or data. For hazards for which the probability of the occurrence of harm cannot be estimated, a listing of the possible consequences of the hazard shall be prepared. The estimate of risk shall be recorded in the risk management file.

Any system used for qualitative or quantitative categorization of probability estimates or severity levels shall be recorded in the risk management file.

NOTE 1. RISK estimation incorporates an analysis of the probability of occurrence and the consequences. Depending on the area of application, only certain elements of the risk estimation process may need to be considered. For example, in some instances it may not be necessary to go beyond an initial hazard and consequence analysis.

NOTE 2. RISK estimation may be quantitative or qualitative.

NOTE 3. Some techniques that can be used for analysis of RISKS are described in Annex xz

NOTE 4. Information or data for estimating risks can be obtained, for example from:

- published standards;
- scientific technical data;
- field data from similar human tissue products already in use including published reported incidents;
- usability tests employing typical users;
- clinical evidence;
- results of appropriate investigations
- expert opinion;
- external quality assessment schemes.

9.5 Risk evaluation (Step 4 of Figure 2)

9.5.1 General

For each identified hazard, the organization shall decide, using the criteria defined in the risk management plan, whether the estimated risks(s) is so low that risk reduction need not be pursued; then 9.5.2 to 9.5.6 do not apply for this hazard (i.e., go to 9.5.7). The results of this risk evaluation shall be recorded in the risk management file.

9.5.2 Risk control (Steps 5-10 of Figure 2)

9.5.2.1 Risk reduction

When risk reduction is required, the organization shall follow the PROCESS in 9.5.2.2 to 9.5.2.7 to control the risks so that the residual risk(s) associated with each hazard is judged acceptable.

9.5.2.2 Option analysis (Step 5)

The organization shall identify risk control measure(s) that are appropriate for reducing the risk(s) to an acceptable level. Risk control shall consist of an integrated approach in which the organization shall use one or more of the following in the priority order listed.

a) inherent safety by design;

b) protective measures in the human tissue product itself or in the manufacturing process;

c) information for safety.

NOTE. Measures of risk control may reduce the severity of the potential harm or reduce the probability of occurrence of the harm or both.

Annex yz addresses inherent, protective and descriptive safety aspects for many human tissue products such as biological safety an microbiological safety and shall be consulted as part of the risk management process.

The risk control measures selected shall be recorded in the risk management file. If, during option analysis, the organization determines that further risk reduction is impractical, the organization shall conduct a risk/benefit analysis of the residual risk (see 9.5.2.4); otherwise, the organization shall proceed to implement the selected risk control measures.

9.5.2.3 Implementation of risk control measure(s) (Step 6)

The manufacturer shall implement the risk control measure(s) selected in 9.5.2.20. The measure(s) used to control the risks shall be recorded in the risk management file.

The effectiveness of the risk control measures shall be verified and the results of the verification shall be recorded in the risk management file.

Implementation of the risk control measures shall be verified. This verification shall also be recorded in the risk management file.

9.5.2.4 Residual risk evaluation (Step 7)

Any residual risk that remains after the risk control measure(s) are applied shall be evaluated using the criteria defined in the risk management plan. The results of this evaluation shall be recorded in the risk management file.

If the residual risk does not meet these criteria, further risk control measures shall be applied (see 9.5.2.2).

If the residual risk is judged acceptable, then all relevant information necessary to explain the residual risk(s) shall be placed in the appropriate accompanying documents supplied by the organization.

9.5.2.5 Risk/benefit analysis (Step 8)

If the residual risk is judged unacceptable using the criteria established in the risk management plan and further risk control is impractical, the organization shall gather and review data and literature on the medical benefits of the intended use/intended purpose to determine if they outweigh the residual risk. If this evidence does not support the conclusion that the medical benefits outweigh the residual risk, then the risk remains unacceptable. If the medical benefits outweigh the residual risk, then proceed to 9.5.2.6 and relevant information necessary to

explain the residual shall be placed in the appropriate accompanying documents supplied by the organization. The results of this evaluation shall be recorded in the risk management file.

9.5.2.6 Other generated hazards (Step 9)

The risk control measures shall be reviewed to identify if other hazards are introduced. If any new hazards are introduced by any risk control measures, the associated risks(s) shall be assessed. The results of this review shall be recorded in the risk management file.

9.5.2.7 Completeness of risk evaluation (Step 10)

The manufacturer shall assure that the risk(s) from all identified hazards have been evaluated. The results of this assessment shall be recorded in the risk management file.

9.6 Overall residual risk evaluation (Step 11 of Figure 2)

After all risk control measures have been implemented and verified, the organization shall decide if the overall residual risk posed by the human tissue product is acceptable using the criteria defined in the risk management plan. If the overall residual risk is judged unacceptable using the criteria established in the risk management plan, the organization shall gather and review data and literature on the medical benefits of the intended use/intended purpose to determine if they outweigh the overall residual risk. If this evidence does not support the conclusion that the medical benefits outweigh the overall residual risk, then the risk remains unacceptable. The results of the overall residual risk evaluation shall be recorded in the risk management file.

9.7 Risk management report (Step 12 of Figure 2)

The results of the risk management process shall be recorded in a risk management report. The risk management report shall provide traceability for each hazard to the risk analysis, the risk evaluation, the implementation and verification of the risk control measures, and the assessment that the residual risk(s) is acceptable. The risk management report shall form part of the risk management file.

NOTE. This report may be held on paper or on electronic media.

9.8 Post-production information (Step 13 of Figure 2)

The organization shall establish and maintain a systematic procedure to review information gained about the human tissue product or similar products in the post-production phase. The information shall be evaluated for possible relevance to safety, especially:

a) if previously unrecognised hazards are present;

b) if the estimated risk(s) arising from a hazard is no longer acceptable;

c) if the original assessment is otherwise invalidated.

If any of the above conditions is satisfied, the results of the evaluation shall be fed back as an input to the risk management process.

In the light of this safety relevant information, a review of the appropriate steps of risk management process for the human tissue product shall be considered. If there is a potential that the residual risk(s) or its acceptability has changed, the impact on previously implemented risk control measures shall be evaluated.

The results of this evaluation shall be recorded in the risk management file.