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Medical products containing viable human cells — Application of risk management and requirements for processing practices

Produits médicaux contenant des cellules viables d'origine humaine — Application du management du risque et exigences relatives aux pratiques de préparation

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Foreword

ISO (the International Organization for Standardization) is a worldwide federation of national standards bodies (ISO member bodies). The work of preparing International Standards is normally carried out through ISO technical committees. Each member body interested in a subject for which a technical committee has been established has the right to be represented on that committee. International organizations, governmental and non-governmental, in liaison with ISO, also take part in the work. ISO collaborates closely with the International Electrotechnical Commission (IEC) on all matters of electrotechnical standardization.

International Standards are drafted in accordance with the rules given in the ISO/IEC Directives, Part 2.

The main task of technical committees is to prepare International Standards. Draft International Standards adopted by the technical committees are circulated to the member bodies for voting. Publication as an International Standard requires approval by at least 75 % of the member bodies casting a vote.

Attention is drawn to the possibility that some of the elements of this document may be the subject of patent rights. ISO shall not be held responsible for identifying any or all such patent rights.

ISO 13022 was prepared by Technical Committee ISO/TC 194, *Biological evaluation of medical devices*, Subcommittee SC 1, *Tissue product safety*.

Introduction

Certain medical products utilize materials of human origin. Depending on national regulatory requirements, these products are addressed as medicinal substances, medical devices or biologics. Materials of human origin are used in the design and manufacture of medical products to provide performance characteristics that might be chosen for their advantages over non-human-based materials, particularly to improve regeneration of the patient's own tissues or organs, or to replace or to supplement organ function.

Medical products utilizing human materials comprise a heterogeneous group. Examples include cell suspensions, cell/matrix constructs or cells combined with complex medical devices such as dialysis equipment.

While the medical products utilizing human material are quite diverse, the hazards specifically related to all human materials are basically the same:

a) the material can be contaminated with infectious agents [e.g. bacteria, moulds, yeasts, viruses, Transmissible Spongiform Encephalopathy (TSE) infectious agents, parasites];

b) the material can be contaminated with chemicals;

c) the material can be unsuitable for the intended purpose due to unintended decomposition or degradation induced by inappropriate handling at any stage of the production process;

d) the material can be hazardous for the patient due to tumorigenic potential;

e) following application, unintended physiological and anatomical consequences can be hazardous, taking into account cell migration and release of biologically active substances;

f) a failure of traceability;

g) the material can cause harm for the patient by eliciting an immunogenic reaction.

To address the hazards related to contamination, degradation, unintended modification and/or mix-up of viable human cells and products, this International Standard was developed for the application of risk management on the manufacture of medical products utilizing viable human material.

The hazards mentioned above have been related to the relevant manufacturing steps. The essential aspects to be covered by this International Standard are as follows:

— terminology and definitions;

— donor selection and testing, addressing both living and deceased donors;

— human material procurement;

— human material handling (including production);

— human material packaging, storage and transport;

— human material labelling;

— risk related to handling of the product during application;

— consideration of risks and benefits in relation to intended use.

This International Standard will assist manufacturers of products based on viable human materials that produce medicinal substances, medical devices or biologics.

Medical products containing viable human cells — Application of risk management and requirements for processing practices

1 Scope

This International Standard specifies requirements and guidance for processing practices and managing risk associated with viable cellular components of products regulated as medicinal products, biologics, medical devices and active implantable medical devices, or combinations thereof. It covers viable human materials of autologous as well as allogeneic human origin, obtained from living or deceased donors.

For manufacturers of medical products containing viable cells of human origin, this International Standard specifies procedures to be used in processing and handling, as well as those to be used in identifying the hazards and hazardous situations associated with such cells, in order to estimate and evaluate the resulting risks, to control these risks, and to monitor the effectiveness of that control. Furthermore, this International Standard outlines the decision process for the residual risk acceptability, taking into account the balance of residual risk and expected medical benefit as compared to available alternatives.

This International Standard provides requirements and guidance on risk management related to the hazards typical of medical products manufactured utilizing viable human materials, such as:

a) contamination by bacteria, moulds, yeasts or parasites;

b) contamination by viruses;

c) contamination by agents causing Transmissible Spongiform Encephalopathies (TSE);

d) contaminating material responsible for undesired pyrogenic, immunological or toxicological reactions;

e) decomposition of the product and degradation products caused by inadequate handling;

f) hazards related to the tumorigenic potential of the cell types used;

g) complications resulting from unintended physiological and anatomical consequences (this includes unintended migration of cells, unwanted release of biologically active substances such as hormones and cytokines, and unintended interactions between cellular and non-cellular components of the product);

h) failure of traceability;

i) complications resulting from the material eliciting an unintended immunogenic reaction.

For the evaluation of contamination with other unclassified pathogenic entities, similar principles might be applicable.

Hazards related to genetic modification are outside the scope of this International Standard and are addressed elsewhere.

NOTE 1 A definition of “genetically modified” can be found in ASTM F2312.

NOTE 2 This International Standard does not specify a quality management system for the control of all stages of production of medical products as described above.

If additional national or regional criteria beyond what is defined in this International Standard exist in the country where the medical product will be used, they are also applicable.

NOTE 3 Regional requirements can be more stringent than requirements referenced in this International Standard, especially with regard to donor eligibility criteria.

This International Standard is not applicable to:

— non-viable materials of human origin;

— viable cells of non-human origin;

— blood and its components used for transfusion, germ cells, organs and bone marrow used for transplantation, and other tissues that do not meet the definition of “medical product”;

— *in vitro* diagnostic devices.

NOTE 4 For guidance on the application of this International Standard, see Annex A.

2 Normative references

The following documents, in whole or in part, are normatively referenced in this document and are indispensable for its application. For dated references, only the edition cited applies. For undated references, the latest edition of the referenced document (including any amendments) applies.

ISO 13485, *Medical devices — Quality management systems — Requirements for regulatory purposes*

ISO 14971, *Medical devices — Application of risk management to medical devices*

ISO 22442-1, *Medical devices utilizing animal tissues and their derivatives — Application of risk management*

ASTM F2312, *Standard Terminology Relating to Tissue Engineered Medical Products*

BSI PAS 84, *Regenerative Medicine — Glossary, June 2008*

3 Terms and definitions

For the purposes of this document, the terms and definitions given in ISO 13485, ISO 14971, ISO 22442-1, ASTM F2312, BSI PAS 84 and the following apply.

3.1
medical device
instrument, apparatus, implement, machine, appliance, implant, *in vitro* reagent or calibrator, software, material or other similar or related article, intended by the manufacturer to be used, alone or in combination, for human beings for one or more of the specific purposes of:

a) diagnosis, prevention, monitoring, treatment or alleviation of disease;

b) diagnosis, monitoring, treatment, alleviation of or compensation for an injury;

c) investigation, replacement, modification, or support of the anatomy or of a physiological process;

d) supporting or sustaining life;

e) control of conception;

f) disinfection of medical devices;

g) providing information for medical purposes by means of *in vitro* examination of specimens derived from the human body;

and which does not achieve its primary intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its intended function by such means

NOTE 1 This definition has been developed by the Global Harmonization Task Force (GHTF).

NOTE 2 Products which could be considered to be medical devices in some jurisdictions but for which there is not yet a harmonized approach are:

a) aids for disabled/handicapped people;

b) devices for the treatment/diagnosis of diseases and injuries in animals;

c) accessories for medical devices (see NOTE 3);

d) disinfection substances;

e) devices incorporating animal and human tissues which can meet the requirements of the above definition but are subject to different controls.

NOTE 3 Accessories intended specifically by manufacturers to be used together with a "parent" medical device to enable that medical device to achieve its intended purpose, should be subject to this International Standard.

NOTE 4 The term "medical devices" covers non-active and active medical devices as well as active implantable medical devices.

NOTE 5 Adapted from ISO 14971:2007, definition 2.9.

3.2
active implantable medical device
active medical device which is intended to be totally or partially introduced, surgically or medically, into the human body or by medical intervention into a natural orifice, and which is intended to remain after the procedure

NOTE 1 An active medical device relies for its functioning on a source of electrical energy or any source of power other than that directly generated by the human body or gravity.

NOTE 2 Adapted from ISO 13485:2003, definition 3.1.

3.3
medicinal product
substance or combination of substances presented as having properties for treating or preventing disease in human beings, or any substance or combination of substances which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis

NOTE See Reference [34].

3.4
medical product
medicinal product, biologic, medical device, or a combination of these

3.5
cell-based medical product
medical product that includes viable human cells of autologous as well as allogeneic human origin, obtained from living or deceased donors, having undergone a manufacturing process

NOTE Cell-based medical products may be combined with non-cellular components.

3.6
biologics
biologicals
cell therapy product of autologous or allogeneic origin in which the cells have been propagated, expanded, selected, pharmacologically treated or otherwise altered in biological characteristics *ex vivo* to be administered to humans and which is applicable to the prevention, treatment, cure, diagnosis or mitigation of disease or injuries

NOTE 1 See Reference [57].

NOTE 2 Clarification of the FDA concerning the definition of biologic can be found at

http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CBER/ucm133077.htm

3.7
donor
human source, whether living or deceased, of human cells or tissues

NOTE In the case of an autologous donation, the living donor is the patient.

3.8
procurement
recovery process by which tissue or cells are obtained from a donor

3.9
residues
substances or materials remaining after production processes such as cell debris, degradation products from a scaffold, chemicals, growth factors, or solvents

3.10
inactivation
process by which the ability to cause infection or pathogenic reaction by a transmissible agent is reduced

NOTE 1 The effectiveness of the process for inactivation of viruses and TSE agents is expressed mathematically in terms of a reduction factor (see ISO 22442-3:2007, Annex F).

NOTE 2 Inactivation aims to prevent infection by, and replication of, transmissible agents.

[ISO 22442-1:2007, definition 3.5]

3.11
manufacture
any or all of the steps in the procurement, screening, testing, processing, storage, labelling, packaging or distribution of any human cellular or tissue-based medical product, including the screening and testing of the cell or tissue donor

3.12
manufacturer
natural or legal person with responsibility for the design, manufacture, packaging and labelling of a cell-based medical product before it is placed on the market under his own name, regardless of whether these operations are carried out by that person himself or on his behalf by a third party

3.13
storage
maintaining the cell-based medical product under appropriate controlled conditions until the time of future processing or distribution

3.14
transport
transferring the cell-based medical product under appropriately controlled conditions

3.15
risk
combination of the probability of occurrence of harm and the severity of that harm

[ISO/IEC Guide 51:1999, definition 3.2]

3.16
harm
physical injury or damage to the health of people, or damage to property or the environment

[ISO/IEC Guide 51:1999, definition 3.3]

3.17
hazard
potential source of harm

NOTE 1 See ICH Q9.

NOTE 2 Adapted from ISO/IEC Guide 51:1999, definition 3.5.

3.18
residual risk
risk remaining after risk control measures have been taken

NOTE 1 Adapted from ISO/IEC Guide 51:1999, definition 3.9.

NOTE 2 ISO/IEC Guide 51:1999, definition 3.9 uses the term “protective measures” rather than “risk control measures”. In the context of this International Standard, “protective measures” are only one option for controlling risk as described in this International Standard.

3.19
risk analysis
systematic use of available information to identify hazards and to estimate the risk

[ISO/IEC Guide 51:1999, definition 3.10]

3.20
risk assessment
overall process comprising a risk analysis and a risk evaluation

[ISO/IEC Guide 51:1999, definition 3.12]

3.21
risk control
process in which decisions are made and measures implemented by which risks are reduced to, or maintained within, specified levels

[ISO 14971:2007, definition 2.19]

3.22
risk estimation
process used to assign values to the probability of occurrence of harm and the severity of that harm

[ISO 14971:2007, definition 2.20]

3.23
risk evaluation
process of comparing the estimated risk against given risk criteria to determine the acceptability of the risk

[ISO 14971:2007, definition 2.21]

3.24
risk management
systematic application of management policies, procedures and practices to the tasks of analysing, evaluating, controlling and monitoring risk

[ISO 14971:2007, definition 2.22]

3.25
risk management file
set of records and other documents that are produced by risk management

[ISO 14971:2007, definition 2.23]

3.26
safety
freedom from unacceptable risk

[ISO/IEC Guide 51:1999, definition 3.1]

3.27
severity
measure of the possible consequences of a hazard

[ISO 14971:2007, definition 2.25]

4 Risk management process

4.1 General

Considerations on risk management shall take into account two components:

a) the probability of occurrence of harm to the patient or user of the product;

b) the consequences of that harm, i.e. how severe it might be.

Risk management is of particular importance to the cellular component of medical products including viable human cells or tissues because of the inherent hazards of this group of products and the variety of stakeholders, including medical practitioners, organizations providing health care, governments, industry, patients and members of the public. Additionally, these stakeholders might be affected by the availability of this type of medical product (the cellular component of a medical product is of particular importance because this raw material can be more rare than other components of a medical product). Therefore lack of availability for the patient is to be considered.

The manufacturer shall make judgments relating to the safety of a cell-based medical product, including the acceptability of risks, taking into consideration the generally accepted state of the art, to determine the suitability of a medical product to be placed on the market for its intended use. This International Standard specifies a process through which the manufacturer of a cell-based medical product can identify hazards associated with the cellular component of the product, estimate and evaluate the risks associated with these hazards, control these risks, and monitor the effectiveness of that control.

The manufacturer shall justify the use of human material (including the choice and source of cell type and/or tissues) based on the residual risk acceptability, considering the balance of residual risk and expected medical benefit, as compared to available alternatives. When considering the risks and benefits of the product, the impact of the surgical procedure required for its administration is to be considered.

The requirements of ICH Q9[20] and Good Manufacturing Practice apply for the medicinal substances part of the product.

The requirements of ISO 14971 and ISO 13485 apply for the medical devices part of the product.

4.2 Hazards associated with the cellular component

4.2.1 General

The manufacturer shall establish, document and maintain throughout the life-cycle of the product a systematic process for identifying hazards associated with the cellular component of a cell-based medical product, estimating and evaluating the associated risks, controlling these risks, and monitoring the effectiveness of the controls. This process shall include the following elements:

a) risk analysis;

b) risk evaluation;

c) risk control;

d) consideration of production and post-production information.

Appropriate parts of the risk management process shall be implemented in the documented product realization process throughout the life-cycle of the product.

NOTE A documented quality management system process can be used by the manufacturer to deal with safety in a systematic manner, in particular to enable the early identification of hazards and hazardous situations in complex cell-based medical products.

Compliance shall be determined by inspection of appropriate documents such as risk management files. Inspection is performed and documented by authorized personnel.

4.2.2 Responsibilities

The manufacturer shall have an organizational structure and operational procedures appropriate to their activities. There shall be an organizational chart which clearly defines accountability and reporting relationships.

The manufacturer shall ensure the availability of adequate resources and of qualified personnel for the manufacture of the product and the risk management activities.

The manufacturer shall:

a) define and document the policy for determining criteria for risk acceptability. This policy shall ensure that criteria are based upon applicable national or regional regulations and relevant International Standards, and consider available information such as the generally accepted state of the art and known stakeholder concerns;

b) review the suitability of the risk management process at planned intervals to ensure continuing effectiveness of the risk management process and document any decisions and actions taken. This review can be part of the quality management system review.

4.2.3 Documentation

4.2.3.1 Risk management activities shall be documented. A suitable means can be a risk management file which includes the risk management plan.

Relevant information included in the risk management plan or its equivalent shall include the following:

a) the scope of the planned risk management activities, identifying and describing the cell-based medical product and the life-cycle phases for which each element of the plan is applicable;

b) assignment of responsibilities and authorities;

c) requirements for review of risk management activities;

d) criteria for risk acceptability, based on the manufacturer's policy for determining acceptable risk, including criteria for accepting risks when the probability of occurrence of harm cannot be estimated;

e) verification activities;

f) activities related to collection and review of relevant production and post-production information.

4.2.3.2 For each identified hazard, the risk management file or its equivalent shall provide traceability to:

a) the risk analysis;

b) the risk evaluation;

c) the implementation, verification and monitoring of the risk control measures;

d) the assessment of the acceptability of any residual risk(s), taking into account considerations of risk and medical benefit in relation to intended use.

4.2.4 Personnel

Personnel directly involved in the activities relating to the manufacture of the cellular component of cell-based medical products shall be qualified to perform such tasks and shall be competent to perform such tasks on the basis of their qualifications, education and training.

4.3 Risk analysis

4.3.1 General

For the risk analysis process, available information is used systematically to identify hazards and to estimate the related risk. For this purpose, all phases of the product life-cycle shall be considered. Particular attention is given to the procurement of cells and/or tissues, all production steps related to this material and, if applicable, the combination partner in the case of combination products.

The implementation of the planned risk analysis activities and the results of the risk analysis shall be recorded in the risk management file or equivalent.

Information on methodological tools for risk identification and evaluation is provided in ISO 14971 and ICH Q9.

4.3.2 Intended use and identification of characteristics related to the safety of the cellular component of the product

The intended use and the contact of the cellular components of a cell-based medical product with the patient's body, or the body of the user, shall be considered. The quantity of material, the contact surface area and the type(s) of the material coming into contact with body tissues or fluids, as well as the type of body tissue or fluid it comes into contact with, shall be addressed in the risk analysis.

Of major importance are critical analyses of:

a) the cell source, addressed in Annexes C, I, J, K and L;

b) the cell type and differentiation status, addressed in Annexes D, E, G, H, K, N, O and P;

c) all aspects of the manufacturing process, addressed in Annexes E, F, G, H, J, L, M, N and P;

d) specific manipulations that might render cells tumorigenic or inadvertently immunogenic, addressed in Annexes E, K, M, N, O and P;

e) the possibility of cross-contamination, addressed in Annexes C, D, F, H, I, J, L, and M;

f) traceability of the material, addressed in Annexes C, D, F, G, H and I;

g) prevention of decomposition, addressed in Annexes D, E, G, H, N, O and P;

h) unintended interaction between cellular and non-cellular components of the product, addressed in Annexes E and O;

i) clinical evaluation and testing, addressed in Annex P.

4.3.3 Identification of hazards

The possible hazards associated with the use of human cells and tissues shall be identified and documented. Particular attention shall be applied to hazards posed by human cells and tissues with regard to:

a) contamination by bacteria, moulds, yeasts or parasites;

b) contamination by viruses;

c) contamination by agents causing TSE;

d) contamination by material responsible for undesired pyrogenic, immunological or toxicological reactions;

e) decomposition of the product and degradation products;

f) lack of reversibility of treatment;

g) hazards related to tumorigenic potential of the cell types used;

h) failure of traceability;

i) complications resulting from unintended physiological and anatomical consequences. This includes unintended migration of cells, unwanted release of biologically active substances such as hormones and cytokines, and unintended interactions between cellular and non-cellular components of the product.

When using stem cells, additional risks might arise. Special attention should be given to tumorigenicity testing and biodistribution assays. Local regulatory requirements for using these cells shall be observed.

For the evaluation of contamination with other unclassified pathogenic entities, similar principles can apply.

4.4 Risk evaluation

All identified risks shall be evaluated. For each identified hazard, the manufacturer shall decide, using the criteria defined in the risk management plan, if risk reduction is required. The results of this risk evaluation shall be recorded in the risk management file or equivalent.

Annex B identifies the main categories of risk that shall be considered.

4.5 Risk control

4.5.1 General

For the control of risk, decisions shall be made and measures shall be implemented by which risks are reduced to, or maintained within, specified levels. The manufacturer shall identify risk control measure(s) that are appropriate for reducing the risk(s) to an acceptable level. The risk control options shall be documented and justified.

The flowchart in Annex B gives an overview of the risk management process. If additional risks are identified during the risk management process, the manufacturer shall choose to follow other relevant standards or regulations. The decision shall be justified and documented.

4.5.2 Residual risk evaluation

After the risk control measures are applied, any residual risk shall be evaluated using the criteria defined in the risk management plan. It is to be checked whether new risks have been introduced by any of the risk mitigation measures. The results of this evaluation shall be recorded in the risk management file or its equivalent.

4.6 Evaluation of overall residual risk acceptability

The evaluation of the overall residual risk acceptability shall consider the balance between the residual risk after implementation of all control measures and the expected medical benefit, as compared to available alternatives. Where residual risks exist with regard to

— contamination by viruses, parasites, bacteria, moulds, fungi or infectious agents causing TSE and/or

— hazards related to tumorigenic or immunogenic potential of the cell types used,

the evaluation shall specifically discuss the risks and benefits of using alternative materials which do not present these risks, such as synthetic materials, materials from other species, or materials of autologous human origin, and applying alternatives for the same intended purposes.

Where residual risks do not meet risk acceptability criteria, the overall risk may only be judged acceptable when balanced by exceptional benefit and feasibility considerations with documented justification.

Evaluation of specific patient populations (e.g. immune compromised) shall be considered if relevant.

4.7 Production and post-production information system

The manufacturer shall establish, document and maintain a system to routinely and systematically collect and review information about risks associated with the application of the cell-based medical product and similar products in the production and the post-production phases. Information gained shall be reviewed, evaluated and the results considered for the review of the risk management process.

NOTE Principles of post-market surveillance and/or pharmacovigilance can be considered.

Annex A
(informative)

Guidance on the application of ISO 13022

A.1 General

Risk management is of particular importance for the cellular component of medical products including viable human cells or tissues because of the particular characteristics of these products. They are highly susceptible to biological contamination and extremely sensitive to all influences causing cell damage and degradation. Therefore it is essential that wherever a risk associated with this material has been identified, the manufacturer takes action to control the risk, or justify in the risk management report why they have not done so.

A.2 Application to sources for human cells and tissues

This International Standard addresses materials such as

a) viable cells and tissues of autologous and allogeneic origin, and

b) viable cells and tissues obtained from living and deceased donors.

A.3 Application to materials supplied by third parties

This International Standard can be applicable when the materials used by manufacturers have been prepared from human sources by third parties or sub-contractors. In considering the risks associated with the use of these products, the manufacturers should seek evidence from their suppliers as to whether relevant requirements of this International Standard have been applied in assessing the suitability of the human material or whether alternative approaches were applied. The information obtained should be incorporated in the risk management report relating to the cell-based medical product, as appropriate, but can be supplemented by information supplied by the third party or sub-contractor.

Annex B
(informative)

Graphic representation of the part of the risk management process for cell-based medical products

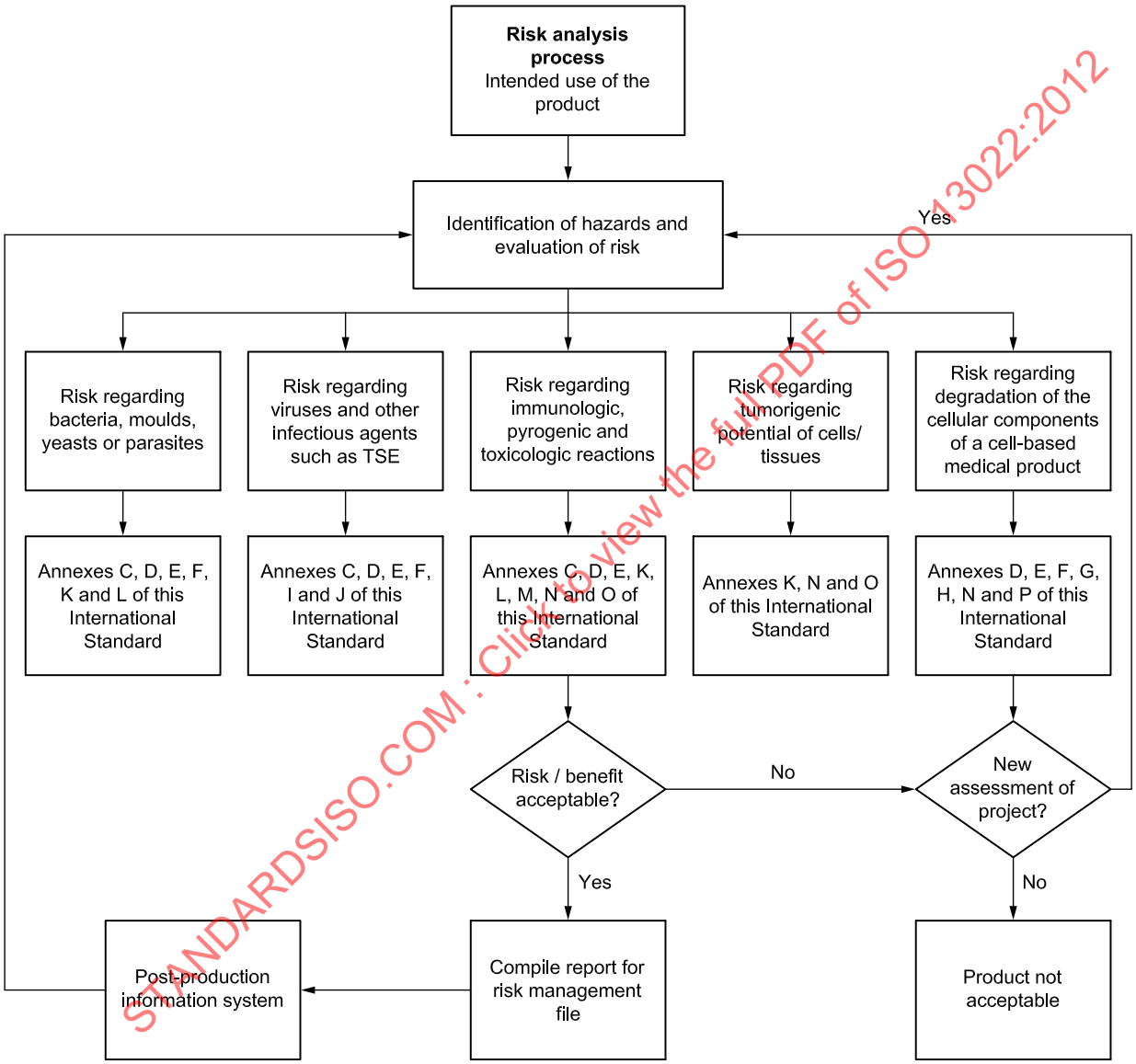

Figure B.1 — Graphical representation of part of the risk management process

Annex C
(normative)

Requirements for donor selection and testing

C.1 General

Selection criteria for donors are based on an analysis of the risks related to the application of the specific cells or tissues and the intended purpose of the cell-based medical product. Indicators of these risks shall be identified by physical examination, review of the medical and behavioural risk history, biological testing, post-mortem examination (for deceased donors) and any other appropriate investigation. Unless justified on the basis of a documented risk assessment approved by the responsible person, donors shall be excluded from donation if any of the criteria listed under C.2.1 applies.

If, in the country where the medical product will be used, there are additional national or regional criteria beyond what is defined in this annex, those criteria apply.

C.2 Deceased donors

C.2.1 General criteria for exclusion

a) Cause of death unknown, unless autopsy provides information on the cause of death and none of the general criteria for exclusion set out in the present section applies.

b) History of a disease of unknown aetiology.

c) Presence, or previous history, of malignant disease. Possible exceptions to this are primary basal cell carcinoma, carcinoma *in situ* of the uterine cervix, and some primary tumours of the central nervous system, which may be acceptable provided that the clinical history of the donor is known.

d) Systemic infection which is not controlled at the time of donation, including bacterial diseases, systemic viral, fungal or parasitic infections, or significant local infection in the tissues and cells to be donated.

e) History, clinical evidence, or laboratory evidence of HIV (human immunodeficiency virus), acute or chronic hepatitis B (except in the case of persons with a proven immune status), hepatitis C and HTLV I/II (Human T-Lymphotropic Virus I/II), transmission risk or evidence of risk factors for these infections.

f) History of chronic, systemic autoimmune disease that could have a detrimental effect on the quality of the cells or tissues to be procured.

g) Indications that test results of donor blood samples will be invalid due to:

   1) the occurrence of haemodilution, where a pre-transfusion sample is not available; or

   2) treatment with immunosuppressive agents.

h) Evidence of any other risk factors for transmissible diseases on the basis of a risk assessment, taking into consideration donor travel and exposure history and local infectious disease prevalence.

i) Presence on the donor's body of physical signs implying a risk of transmissible disease(s).

j) Ingestion of, or exposure to, a substance (such as cyanide, lead, mercury, gold) that can be transmitted to recipients in a dose that could endanger their health.

k) Recent history of vaccination with a live attenuated virus where a risk of transmission is considered to exist.

l) Transplantation with xenotransplantation products.

m) Risk of transmission of diseases caused by a TSE infectious agent. This risk applies, for example, to:

1) people diagnosed with Creutzfeldt–Jakob disease, or variant Creutzfeldt-Jakob disease, or having a family history of non-iatrogenic Creutzfeldt-Jakob disease;

2) people with a history of rapid progressive dementia or degenerative neurological disease, including those of unknown origin;

3) recipients of hormones derived from the human pituitary gland (such as growth hormones) and recipients of grafts of cornea, sclera and *dura mater*, and persons that have undergone undocumented neurosurgery (where *dura mater* may have been used). For variant Creutzfeldt-Jakob disease, further precautionary measures are recommended.

C.2.2 Additional criteria for deceased child donors

Any children born from mothers with HIV infection or that meet any of the exclusion criteria described above shall be excluded as donors until the risk of transmission of infection can be definitely ruled out.

Children aged less than 18 months born from mothers with HIV, hepatitis B, hepatitis C or HTLV I/II infection, or at risk of such infection, and who have been breastfed by their mothers during the previous 12 months, cannot be considered as donors regardless of the results of the analytical tests.

Children of mothers with HIV, hepatitis B, hepatitis C or HTLV I/II infection, or at risk of such infection, and who have not been breastfed by their mothers during the previous 12 months and for whom analytical tests, physical examinations, and reviews of medical records do not provide evidence of HIV, hepatitis B, hepatitis C or HTLV I/II infection, can be accepted as donors.

C.3 Living donors – General criteria for selection

C.3.1 Autologous living donor: If the removed tissues and cells are to be stored or cultured, the same minimum set of biological testing requirements shall apply as for an allogeneic living donor. Positive test results will not necessarily prevent the tissues or cells or any product derived from them being stored, processed and reimplanted, if appropriate isolated storage facilities are available to ensure no risk of cross-contamination with other grafts and/or no risk of contamination with adventitious agents and/or mix-ups.

C.3.2 Allogeneic living donor: Allogeneic living donors shall be selected on the basis of their health and medical history, which is provided on a questionnaire and through an interview performed by a qualified and trained medical professional with the donor. This assessment shall include relevant factors that can assist in identifying and screening out persons whose donation could present a health risk to others, such as the possibility of transmitting diseases or health risks to themselves. For any donation, the collection process shall not interfere with or compromise the health or care of the donor. In the case of cord blood or amniotic membrane donation, this applies to both mother and baby.

Selection criteria for allogeneic living donors shall be established and documented by the tissue establishment (and the transplanting clinician in the case of direct distribution to the recipient), based on the specific tissue or cells to be donated, together with the donor's physical status and medical and behavioural history and the results of clinical investigations and laboratory tests establishing the donor's state of health.

The pre- or post-partum donation of cells should require evaluation of the baby for relevant risk during the post-partum visit. For cord blood collected before or after the delivery, and amniotic membrane, the mother should be considered as the donor.

The same exclusion criteria shall be applied as for deceased donors with the exception of C.2.1 a). Depending on the tissue or cell to be donated, other specific exclusion criteria can be added, such as:

a) pregnancy (except for donors of umbilical cord blood cells and amniotic membrane and sibling donors of haematopoietic progenitors);

b) breastfeeding;

c) in the case of haematopoietic progenitor cells, the potential for transmission of inherited conditions.

C.4 Biological tests required for donors

The following biological tests shall be performed for all donors as a minimum requirement:

a) HIV 1 and 2 – Anti-HIV-1,2;

b) Hepatitis B – HBsAg (Hepatitis B surface antigen), HBc (Anti Hepatitis B core antigen);

c) Hepatitis C – Anti-HCV-Ab (Hepatitis C virus antibody);

d) Syphilis – See below.

Human T-lymphotrophic virus (HTLV)-I/II antibody testing shall be performed according to national regulations.

When anti-HBc is positive and HBsAg is negative, further investigations are necessary with a risk assessment to determine eligibility for clinical use.

A validated testing algorithm shall be applied to exclude the presence of active infection with *Treponema pallidum*. A non-reactive test, specific or non-specific, can allow tissues and cells to be released. When a non-specific test is performed, a reactive result will not prevent procurement or release if a specific *Treponema* confirmatory test is non-reactive. A donor whose specimen tests are reactive on a *Treponema*-specific test requires a thorough risk assessment to determine eligibility for clinical use.

Additional testing can be required depending on the donor's history and the characteristics of the tissue or cells donated, e.g. RhD (Rh blood group D antigen), HLA (Human Leukocyte Antigen), malaria, CMV (cytomegalovirus), toxoplasma, EBV (Epstein-Barr virus), *Trypanosoma cruzi*.

For autologous donors, C.3.1 applies.

C.5 Requirements to be met for determining biological markers

C.5.1 General

The tests shall be carried out by a qualified laboratory.

NOTE A qualified laboratory is accredited, licensed, registered or authorized according to local requirements.

The type of test used shall be validated for the purpose in accordance with current scientific knowledge. The biological tests shall be carried out on the donor's serum or plasma; they shall not be performed on other fluids or secretions such as the aqueous or vitreous humour unless specifically justified clinically using a validated test for such a fluid.

C.5.2 Haemodilution

When potential donors have lost blood and have recently received donated blood, blood components, colloids or crystalloids, blood testing might not be valid due to haemodilution of the sample. An algorithm shall be applied to assess the degree of haemodilution in the following circumstances:

— ante-mortem blood sampling: if blood, blood components and/or colloids were infused in the 48 h preceding blood sampling, or if crystalloids were infused in the hour preceding blood sampling;

— post-mortem blood sampling: if blood, blood components and/or colloids were infused in the 48 h preceding death or if crystalloids were infused in the hour preceding death.

Tissue establishments may accept tissues and cells from donors who have been tested for required infectious diseases using a blood sample that is suspected to be diluted more than 50 % only if the tests are validated for use with such a sample, or a sample is available that was taken before transfusion/infusion.

C.5.3 Sampling from deceased donors

In the case of a deceased donor, blood samples shall have been obtained just prior to death or, if this is not possible, the time of sampling shall be within 24 h of death.

C.5.4 Sampling from living donors

a) In the case of living donors (except allogeneic bone marrow stem-cell and peripheral blood stem-cell donors, for practical reasons), blood samples shall be obtained at the time of donation or, if not possible, within 7 d post donation (this is the “donation sample”).

b) If tissues and cells of allogeneic living donors can be stored for long periods, repeat sampling and testing is required after an interval of 180 d. In these circumstances of repeat testing, the donation sample can be taken up to 30 d prior to and 7 d post donation.

c) Where tissues and cells of allogeneic living donors cannot be stored for long periods and repeat sampling is therefore not possible, point a) applies.

If in a living donor (except bone marrow stem-cell and peripheral blood stem-cell donors) the “donation sample”, as defined under a) is additionally tested by the nucleic acid amplification technique (NAT) for HIV 1 and 2, HBV (Hepatitis B virus) and HCV, testing of a repeat blood sample in accordance with b) is not required. Retesting is also not required if the processing includes an inactivation step that has been validated for the viruses concerned.

In the case of bone marrow and peripheral blood stem-cell collection, blood samples shall be taken for testing within 30 d prior to donation.

In the case of neonatal donors, the biological tests can be carried out on the donor’s mother to avoid medically unnecessary procedures on the infant.

Annex D
(informative)

Guidance for tissue procurement

D.1 General

Cell and tissue material should only be obtained from properly identifiable donors with informed consent. Special considerations apply for autologous, living and deceased donors.

D.2 Consent and donor identification

Before the procurement of tissues and cells proceeds, consent for the procedure should be obtained and documented showing how and by whom the donor has been reliably identified.

D.3 Donor evaluation for allogeneic donors

The donor's relevant medical and behavioural information in accordance with the requirements described in D.5 should be collected and recorded.

To acquire the appropriate information, different relevant sources should be used, including at least an interview with the donor, for living donors, and the following when appropriate:

a) the medical records of the donor;

b) an interview with a person who knew the donor well (for deceased donors);

c) an interview with the treating physician;

d) an interview with the general practitioner;

e) the autopsy report.

In addition, in the case of a deceased donor, and in the case of a living donor when justified, a physical examination of the body should be performed to detect any signs that may be sufficient in themselves to exclude the donor or which should be assessed in the light of the donor's medical and personal history. The complete donor records should be reviewed and assessed for suitability and signed by a qualified health professional.

D.4 Procurement procedures for tissues and cells

The procurement procedures should be appropriate for the type of donor and the type of tissue or cells donated. There should be procedures in place to protect the safety of the living donor. The procurement procedures should protect those properties of the tissue or cells that are required for their ultimate clinical use, and at the same time minimize the risk of microbiological contamination during the process.

For deceased donation, the area of access should be restricted. A local sterile field using sterile drapes should be used. Staff conducting procurement should be clothed appropriately for the type of procurement. Usually, this will extend to being scrubbed, gowned in sterile clothing and wearing sterile gloves, face shields and protective masks.

In the case of a deceased donor, the place of procurement should be recorded and the time interval from death to procurement should be specified so as to ensure that the required biological and/or physical properties of the tissues or cells are retained.

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

Policies and procedures should be in place to minimize the risk of tissue or cell contamination by staff who might be infected with transmissible diseases.

Sterile instruments and devices should be used for tissue and cell procurement. Instruments or devices should be of adequate quality, validated or specifically certified and regularly maintained for the procurement of tissues and cells. When re-useable instruments are used, compliance with a validated cleaning and sterilization process for removal of infectious agents should be documented. A system should be in place that allows tracing of all procurement instruments or devices to the donor, or the tissue or cells procured.

All relevant staff should have received appropriate training on the use of such devices. Records should be kept that show that all relevant staff have received appropriate training on the use of such devices.

D.5 Donor documentation

D.5.1 For each donor, there should be a record containing:

a) the donor's identity, i.e. first name, family name and date of birth (if a mother and child are involved in the donation, both the name and date of birth of the mother and the name, if known, and date of birth of the child);

b) age, sex, medical and behavioural history (the information collected should be sufficient to allow application of the exclusion criteria, where required);

c) time since death until procurement;

d) outcome of body examination, where applicable;

e) haemodilution formula, where applicable;

f) the consent/authorization form, where applicable;

g) clinical data, laboratory test results, and the results of other tests carried out;

h) the results of the autopsy, if performed (for tissues and cells that cannot be stored for extended periods, a preliminary verbal report of the autopsy should be recorded);

i) for haematopoietic progenitor cell donors, the donor's suitability for the chosen recipient;

j) for unrelated donations, when the organization responsible for procurement has limited access to recipient data, the transplanting organization should be provided with donor data relevant for confirming suitability.

D.5.2 The organization performing the procurement should produce a procurement report which is passed on to the tissue establishment. This report should contain at least:

a) the identification, name and address of the tissue establishment to receive the cells or tissues;

b) donor identification data (including how and by whom the donor was identified);

c) description and identification of procured tissues and cells (including samples for testing);

d) identification of the person who is responsible for the procurement session, including signing;

e) date, time (where relevant, start and end) and location of procurement, and the standard operating procedure used, including any incidents that occurred; where relevant, environmental conditions at the procurement facility (description of the physical area where procurement took place);

f) for deceased donors, conditions under which the cadaver is kept, i.e. refrigerated (or not), time of start and end of refrigeration;

g) ID/batch numbers of reagents and transport solutions used.

The report should also contain the date and time of death. All the records should be clear and readable, protected from unauthorized amendment and retained and readily retrieved in this condition throughout their specified retention period in compliance with data protection legislation.

Annex E
(normative)

Requirements for handling of cells and tissue during manufacture

E.1 General

The manufacturing process of cell-based medical products shall be carefully designed and validated to ensure product consistency. All requirements shall be defined and justified.

If, in the country where the medical product will be used, there are additional national or regional requirements beyond what is defined in this annex, those apply.

NOTE Guidance on special requirements for handling of cells and tissue during manufacture can be found in References [38] and [46].

E.2 Specifications

Specifications are required for the cells or tissues used, all production aids, intermediates and the medical product. Specifications shall be documented.

E.3 Documentation

A documented procedure with a detailed description of the manufacture of the cellular components and of the finished product is required. The type of manipulation(s) required for cell processing and the maintenance of the physiological function of the cells shall be described. A flow diagram of the entire process starting from the biological fluid, tissue or organ, or from cell banks, shall be prepared indicating critical steps and intermediate products (e.g. intermediate cell batches), as well as operating parameters, in-process controls and acceptance criteria.

E.4 Combined cell-based medical products

Manufacture of medical products consisting of cells and matrices/devices/scaffolds require additional consideration regarding the cell/matrix/scaffold interactions and quality issues related to these components.

Matrices/devices/scaffolds shall comply to their appropriate regulations and standards.

Attention shall be paid to biodegradable materials, which can for example possess the potential for environmental changes (e.g. raising pH) for the cells during manufacture or after administration.

E.5 Manufacturing area

The manufacturing area shall be physically separated from the procurement area. If different tissues and cellular products are processed in the same manufacturing area, there is an increased risk of cross-contamination during each step of the procedure, e.g. via processing equipment. Therefore, adequate cleaning and control measures to prevent cross-contamination shall be put in place.

Equipment and premises used for manufacturing of cell-based medical products shall be suitable and qualified for aseptic production. It is recommended that dedicated, product-specific or single-use equipment is used in the production, whenever possible.

For requirements concerning the procurement, see Annex D.

E.6 Cell handling procedures

E.6.1 General

All cell handling procedures shall be justified in terms of their intended purpose. The impact of the manipulation of the cells or tissue on any stage of the manufacturing process is to be considered in the risk management process. The significance of changes (e.g. cell source, raw materials, manufacturing platforms, manufacturing sites) needs particular attention.

All cell procedures shall be carried out according to documented standard operating procedures. The different process steps shall be validated. Relevant controls shall be defined. Microbiological control is a pivotal aspect of the process control and risk management of all cell preparations. Monitoring of *in vitro* cell culturing at selected stages of the production shall be performed where feasible. The culture shall be examined for any microbial contamination in accordance with the culturing procedure and growth characteristics of the cells.

Guidance on special requirements for handling of cells and tissue during manufacture can be found in Reference [38].

E.6.2 Organ/tissue dissociation

The procedure to dissociate the organ and/or tissue shall be described with respect to the technique used, the enzyme, and the media applied. Consideration shall be given to the degree of disruption applied to the tissue in order to preserve the intended functional integrity of the cellular preparation and to minimize cell-derived impurities in the product (cell debris, cross contamination with other cell types).

Careful consideration shall be given to the controlled environment were organ/tissue dissociation is performed. It can be useful to use a class A laminar flow hood.

E.6.3 Isolation of the cell population of interest

The procedure used to isolate and/or purify and/or enrich the cell population of interest shall be appropriately documented. The process, including equipment and reagents, is to be validated with regard to the effectiveness of the process in obtaining the cell population of interest.

E.6.4 Cell culture

The procedure used to culture the cells or tissue shall be described. The process is to be validated and its effectiveness is to be addressed in relation to the intended use. The processing steps shall be properly designed to preserve the integrity and function of the cells. Any manipulation during culture shall be documented in detail and closely monitored according to specified process controls. The duration of cell culture and maximum number of cell passages shall be clearly specified and validated. The relevant genotypic and phenotypic characteristics of the primary cell cultures, of the established cell lines and the derived cell clones shall be defined and their stability with respect to culture longevity determined. Consistency and repeatability of the cell culture process shall be demonstrated and the culture conditions including the media and the duration shall be optimized, defined and validated with respect to the intended clinical function of the product.

Special consideration shall be given to the growth potential of cells in response to added growth factors since cell subpopulations may gain a growth advantage under defined *in vitro* culturing conditions.

Analysis of literature data may be used to evaluate whether propagation of viral contaminants during cell culture needs consideration.

E.6.5 Cell modification

Various treatments (e.g. physical, chemical and/or genetic) can be applied to cells. The method used to modify the cells shall be fully described. The process is to be validated and its effectiveness is to be addressed in relation to the intended use.

In the case of genetic modification of cells, relevant standards and guidelines apply.

E.6.6 Cells cultured in or on a matrix/device/scaffold

If the cells are grown directly inside or on a matrix/device/scaffold, the quality of the combined cell-based medical product relies on the properly controlled manufacturing process (see E.1 to E.5) and the quality of the combination partner. For such products, the effect of the matrix/scaffold/device on the cell growth, function and integrity shall be taken into account. The effect that the cells can exert on the device (e.g. on rate of degradation) shall also be considered (see also Annex M).

E.7 In-process controls

The manufacturing process shall be controlled by in-process controls at the level of critical steps or intermediate products. Intermediate cell or tissue products are products that can be isolated during the process; specifications of these products shall be established in order to assure the reproducibility of the process and the consistency of the final product. Tests and acceptance criteria shall be described.

E.8 Batch definition

The purpose of the batch definition is to ensure consistency and traceability. A clear definition of a production batch from cell or tissue sourcing to the labelling of the final container shall be provided (i.e. size, number of cell passages/cell duplications, pooling strategies, batch numbering system). In the autologous setting, the manufactured product shall be viewed as a batch.

Annex F
(normative)

Requirements for packaging and labelling

F.1 General

All procured cells and tissues, intermediates and the final product shall be stored and packed sterile to minimize the risk of contamination and degradation. The containers used shall be suitable for storage and transportation of the relevant biological material. The containers shall protect and preserve the safety and quality of the tissue contained therein. Specifications for all parts of the packaging shall be set up.

F.2 Specifications

Specifications are required for all the packaging components (e.g. the container closure system and primary packaging, secondary and external packaging). Specifications shall be documented.

F.3 Documentation

Detailed descriptions of the packaging process(es) and the materials are required.

F.4 Chemical properties of the packaging container

Primary packaging and materials that are in direct contact with the tissue shall be qualified. Medical devices may be the preferred container system due to their biocompatibility and quality control requirements; however, such controls might not be sufficient and should be justified. Contamination of the product by leachables or extractables from the packaging material by toxicological, immunological or pyrogenic substances is to be avoided by any means.

The container shall also be inert to the product (e.g. dimethyl sulfoxide in the product is prone to causing leachables in certain container systems).

F.5 Physical properties of the packaging container

The containers shall prevent degradation of the cells, tissue or the final product due to environmental conditions (e.g. temperature, light).

F.6 Contamination

The packaging shall prevent contamination originating from persons responsible for packaging and transportation of the tissue.

F.7 Labelling

F.7.1 To ensure traceability and unequivocal identification of tissues or cells or the final product, all transport containers shall be labelled.

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

The primary container holding the tissue shall, as a minimum requirement, bear a label specifying the donor's identity and/or donor code, and the type of tissue within the container. If the primary container is large enough, it should bear a label including the following data:

a) donor identity and/or donor code, and type of tissue;

b) date and, if possible, time of procurement;

c) hazard warnings;

d) nature of any additives (if used);

e) in the case of autologous donation the label shall state "for autologous use only"; in the case of directed donations, the label shall identify the intended recipient.

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

F.7.2 If the tissue is transported by a third party (e.g. a forwarding company) each transport container shall be labelled with at least the following information:

a) "Caution", "Tissues and Cells" and "Handle with Care" labels;

b) identification of the establishment from which the package originates (including address and telephone number) and name of a person at the originating establishment or designee to be contacted in the event of problems;

c) identification of the processing company, tissue bank, or other destination establishment (including address and telephone number) and name of a person or designee to be contacted to take delivery of the container;

d) date and time of the start of transportation specifications regarding the transportation conditions necessary to maintain safety and quality of the tissue or cells;

e) the additional text "Do not irradiate";

f) if it is known that the donor is positive for a relevant infectious disease marker, the following text shall be added: "Biological Hazard";

g) in the case of autologous tissue or cell donations, the following text shall be added: "For autologous use only";

h) any additional specifications regarding storage conditions (e.g. "Do not freeze").

F.8 Requirements for primary packaging

F.8.1 Primary packaging used after the procurement or during the process (intermediaries or finished products)

Following procurement or other steps of the production process, all tissues and cells, intermediates that include cells, or the finished product shall be packaged in a manner which minimizes the risk of contamination. They shall be stored at temperatures that preserve the required characteristics and biological function of the cells or tissues. The packaging shall also prevent contamination of those responsible for packaging and transportation of the tissues and cells. The primary packaging comprises a sterile and tight container which is adequate for the product and validated for the use for which it is intended.

Preferably, the primary packaging should be a medical device (see F.4). The user will have to validate the container system selected, in order to make sure that it meets the fixed specifications, in particular, in terms of physical security (if necessary, resistance to low temperatures), chemical properties (absence of interaction with the products in contact) and microbiological requirements (sterility and absence of pyrogenic material).

A description of the container closure system should be provided. Compatibility of the system with the product should be demonstrated. Information on the sterilization procedures of the container and the closure should be provided. Additional data may be required if packaging components are used in the transport and/or application procedure.

F.8.2 Primary packaging of the blood samples obtained from the donor

Blood samples are collected from the donor of cells and tissues in order to perform relevant laboratory tests. The packaging used for the procurement and the storage of the blood samples in a serum library shall be validated as being suitable for the purpose. Any accompanying tissue or blood samples for testing shall be accurately labelled to ensure identification with the donor, and shall include a record of the time and place the specimen was taken.

F.8.3 Primary packaging of the samples used for the quality control of the products

The packaging used for collection and storage of samples from procurement, intermediaries or finished product intended for quality control shall be tight and suitable for the nature of the sample and the analysis. In particular, the type of container, its closure system, type and quantity or concentration of ancillary materials (medium), if applicable, shall be specified as necessary for the intended sample. The packaging shall be validated as adequate for the intended use. Differences in packaging used for product and samples for quality control should be justified.

F.9 Shipping container

The packaged cells or tissues shall be shipped in a container which is suitable for the transport of biological materials and which maintains the safety and quality of the tissue or cells contained within it. This packaging is mandatory for all products of human origin at all steps of transportation and is essential for some of these products during procurement, processing and storage in order to maintain the guarantee of asepsis conditions of the primary packaging (e.g. double packaging of the femoral heads).

For the transport of product in the liquid state, external packaging shall be hermetic, and an absorbing material shall be placed in sufficient quantity in the container in order to avoid any possible escape of liquid. The primary and external packaging should be in a transport container. The usual accompanying documents can be placed between the external and the transport container. The shipping container shall be impact-resistant, maintain the sterility of the primary packaging and be tamper-proof.

Whatever the status of the transported product (procurement, intermediate product or finished product), the labelling of the container shall include the information as detailed in F.7.

F.10 Packaging of waste products with biological risk resulting from the procurement or the processing

Potentially contaminated or contaminated wastes shall be placed in single containers, sealed tight, labelled adequately and prepared for incineration. For potentially contaminated liquid waste, the container shall contain a disinfectant.

Annex G
(informative)

Guidance for transport

G.1 General

This annex provides guidance for the transport of procured cells or tissue, intermediates and the transport of the final product.

All transport activities should take place under safe and controlled conditions, which ensure preservation of the cell, tissue and product properties necessary for the intended use, and prevent degradation and contamination of the product. The chosen modes of transportation should be suitable for the purpose with regard to the biological and logistical requirements. The mode of transport should be validated. It should be specified in writing in accordance with national legislation.

The transportation methods described in this International Standard apply to international or national transport operations by the manufacturer, or on account of the manufacturer, without prejudice to regulations that are in force relating to the transport of the infectious matters [e.g. IATA (International Air Transport Association), ADR (Accord Européen Relatif au Transport International des Marchandises Dangereuses par Route)], of the products defined below:

a) tissues, cells, blood samples resulting from the donor's procurement;

b) samples for internal and external quality control of tissues,

c) cells for the biological product library and the serum library.

The guidelines described in this annex are not applicable to the transport of waste with a biological risk, nor to the transport of samples for environmental controls of the facilities where the process is carried out.

The product should be transported under conditions that:

1) ensure its safe storage and its integrity;

2) ensure its shipment within a defined time;

3) comply with hygiene and security requirements with respect to the environment and the persons in charge of transport.

This annex applies to the following operations:

— preparation of the container;

— shipping (or transport itself);

— reception of the products by the manufacturer and user.

G.2 Specifications

Transport specifications should determine the type of transport container and the way it is identified, as well as the inclusion of samples, if any, and the procurement report to the processing company.

G.3 Validation

The operational validation of tissue transport should take into consideration requirements relating to the internal temperature of the container, environmental temperature, as well as other biological, chemical and physical parameters relevant for the protection of the cells or tissues or the product. Seasonal temperature fluctuations should be taken into account, if applicable. If, for example, the tissue or product should be maintained within a particular temperature range during transport, it is recommended that a suitable and qualified temperature sensor be placed inside the package to monitor and document internal temperatures.

Transport times should be specified in the predetermined terms and conditions of transport, which ensure the retention of the necessary cell and tissue properties.

When carbon dioxide in solid form or nitrogen in liquid form are added in the container, or when accumulators of cold or heat eutectics are used, those should be in a sufficient quantity to maintain within the container the desired temperature for twice the length of time estimated at the beginning. Their position within the container should maintain a temperature homogeneous in the whole of the volume of the container.

G.4 Documentation

Dates and, if relevant, times of package collection at the procurement organization and delivery to the manufacturer or processing company should be documented.

G.5 Cross-contamination

During transport, access to the package and its contents by unauthorized third parties should be prevented. If necessary, a sealable outer transport container should be used. Variances or incidents occurring during transport should be reported to the procurement organization and the manufacturer or processing company.

G.6 Contractual agreements

Transport contracts should be concluded with qualified forwarding companies. The forwarding company should ensure full compliance with the specified, validated transport conditions. Procurement organizations can put the manufacturer, the processing company, or third parties in charge of transportation of procured tissue or cells. In such cases, written agreements should be established, specifying the responsibilities of the third parties and detailed procedures to be followed.

G.7 Preparation of the transport container

Procedures should be set up defining the following:

a) the conditions of preparation of the container;

b) labelling of the container;

c) the instructions to be given for transport;

d) the documents to be given to the person in charge of transport.

In cases where the transport containers hold liquids, carbonic ice or liquid nitrogen, labelling and documentation should be in conformity with specific written requirements envisaged in these cases.

The shipper establishment or the manufacturer should check the conformity of the transport container with the relevant specifications.

G.8 Transport of the products

An explicit agreement is required between the shipper and the recipient establishment detailing the responsibility for all aspects of the transport process.

With regard to schedule and routing, instructions should be established concerning:

a) means of transport (including e.g. specific equipment, maintenance, hygiene);

b) routes and routing times;

c) control of the relevant environmental parameters, e.g. temperature.

G.9 Responsibilities of the manufacturer

The manufacturer should perform all of the operations related to the transport of raw materials to finished product. These tasks can also be delegated to one or more subcontractors. It is the responsibility of the manufacturer to check whether the subcontractor is qualified to perform the task.

When transport is carried out by the manufacturer, it should be performed according to procedures detailing the packaging of the products to be transported, the conditions and means for the transport, the routes, the maximally allowed delay between the shipment and the delivery, the responsibilities for each person involved in the transport, and control at the delivery. The conditions of transport should be chosen taking into account the safety criteria and the conditions of storage suitable for the transported products.

The personnel in charge of transport should receive adequate instructions with regard to related risks (e.g. infectious diseases) and the type of products transported. Standard operating procedures should be set up describing clearly the measures to be taken to protect the product and the person in charge of the transport.

When an emergency case justifies the exceptional need for a subcontractor who has not been qualified in advance, the manufacturer should give precise written instructions to the subcontractor for the required transport conditions for the product.

G.10 Material and hygiene

The material and equipment used for the transport of products (e.g. vehicles, temperature-controlled enclosures, containers) should be suitable for the purpose and qualified if necessary with regard to the specified requirements of transport of each type of product. In particular, duration of transport, maintenance of the required temperatures of storage during transport, dedicated or gathered transport, hygiene and security should be considered. Material and equipment should be the subject of maintenance on a regular basis, carried out according to procedures.

Any defective material or equipment should be withdrawn from the logistics chain or, at least, clearly labelled as such while waiting for repair or removal.

The data logger for the monitoring of the temperature should be of an appropriate range and with appropriate precision details as to the temperatures of storage and transport of the products. They should be calibrated and checked at regular intervals.

The transport containers and reusable secondary packaging should be kept clean and should be subjected to cleaning and decontamination, as described in procedures.

Vehicles being used for road transport should be cleaned regularly and decontaminated in case of contamination by the product.

G.11 Packaging and labelling of the transport container

See the information given in Annex F.

G.12 Documents relating to transport

A special transport form should be provided to the conveyor or its representative at the same time that the container is provided.

In preparation for any accident or incident which can occur during transport, precise instructions should be given to the conveyor, clearly specifying:

a) the nature of the danger presented by the products transported, as well as the safety measures to be taken to face them;

b) measures to be taken for personnel and the product in the event of breakage or deterioration of the packaging, in particular when the products spread outside the packaging.

These instructions should include the person to be contacted [name, addresses and telephone number(s)].

G.13 Transport conditions and duration

The transport of the cell-based products should be carried out as soon as possible. The duration and condition of transport should be controlled either by a system which guarantees the maintenance of the temperature or by precise knowledge of the steps of transport (in particular, delay and conditions of storage). This control includes in particular:

a) knowledge of the estimated duration of transport according to the destination;

b) knowledge of the route between the shipping establishment and the destination of the products and eventually the intermediate area of storage before the product arrives at its final place of storage.

G.14 Delivery and control at reception

Compliance with the specified transport conditions should be checked in particular in relation to:

a) the integrity of the container and label;

b) the conditions of monitoring of the relevant environmental parameters (e.g. temperature) during transport;

c) the duration of transport.

Any anomalies or non-conformity raised during the transport should be documented. If deviations have been recorded, it is recommended that this information be forwarded to the conveyor and to the shipping establishment or company. Investigations to determine the causes should be carried out and corrective and preventive actions should be taken.

G.15 Reception of the tissue and cells

When the tissues or cells arrive at the tissue establishment, there should be documented verification that the consignment, including the transport conditions, packaging, labelling and associated documentation and samples, meet the requirements of this International Standard and the specifications of the receiving establishment.

Each establishment should ensure that the tissue and cells received are quarantined until they, along with the associated documentation, have been inspected or otherwise verified as conforming to requirements. The review of relevant donor and procurement information, and thus acceptance of the donation, should be carried out by specified persons.

Each tissue establishment should have a documented policy and specifications against which each consignment of tissues and cells, including samples, are verified. These should include the technical requirements and other criteria considered by the tissue establishment to be essential for the maintenance of acceptable quality. The tissue establishment should have documented procedures for the management and segregation

of non-conforming consignments, or those with incomplete test results, to ensure that there is no risk of contamination of other tissues and cells being processed, preserved or stored.

The data to be registered at the tissue establishment should include:

a) consent/authorization, including the purpose(s) for which the tissues and cells may be used (i.e. therapeutic or research, or both therapeutic use and research) and any specific instructions for disposal if the tissue or cells are not used for the purpose for which consent was obtained;

b) all required records relating to the procurement and the taking of the donor history, as described in D.5;

c) results of physical examination, laboratory tests and other tests (such as the autopsy report);

d) for allogeneic donors, a properly documented review of the complete donor evaluation against the selection criteria by an authorized and trained person;

e) in the case of cell cultures intended for autologous use, documentation of the possibility of medicinal allergies (such as to antibiotics) of the recipient.

Annex H
(informative)

Guidance for storage

H.1 General

This annex is applicable to both the requirements for storage of donated cells or tissues and of the cellular component of the final product.

Donated cellular material, once processed, may be:

a) a single primary cell isolate used directly for the cell-based medical product;

b) primary cells cultured for a few passages before being used for the cell-based medical product;

c) cells based on a well-defined cell bank system consisting of seed lot, working seed lot, a master cell bank and a working cell bank.

Procedures for the control of storage areas should be established and applied, in order to prevent any situation arising that might adversely affect the functionality or integrity of tissues and cells. All storage processes should be carried out under controlled conditions.

Storage conditions should ensure cell viability, density, purity, sterility, function and potency.

An adequately controlled cell storage system should be established to allow proper maintenance and retrieval of cells, tissues and the cell-based medical product without any alteration of their intended final characteristics. Identity should be verified by relevant genotypic and/or phenotypic markers and the proportion of cells bearing these identity markers evaluated as an indicator of the intended cell population.

H.2 Facility

The storage facility should be of sufficient size with secure access. It should be established and maintained in order to guarantee the quality and the traceability of the stored products. The facility should be clean and dry. If necessary, defined limits of temperature and humidity should be controlled.

H.3 Personnel

Access to the facility should be restricted to adequately trained and approved personnel.

H.4 Specification

Storage conditions should be specified to guarantee the quality of the cells or tissues with regard to cell identity, purity, viability and functionality. Contamination with microbiological contaminants should be prevented. Cross-contamination with cells or nucleic acid of other origin should be prevented.

H.5 Qualification and validation

Storage equipment or devices should be qualified and storage conditions subject to validation.

It is recommended that records be maintained that qualify equipment or devices used for storage of tissues and cells. Specifications selected for storage equipment should establish confidence that it is capable of maintaining the required, controlled environment. A procedure detailing the required conditions, responsibilities

and specifications for the validation of each type of tissue and cell for their storage, transfer or distribution, should exist.

The maximum storage time should be specified for each type of storage condition based on real time (and, if applicable, accelerated) stability data using adequate test methods. The selected period should be bound, among other things, by the possible deterioration of the functional properties of tissues and cells.

H.6 Monitoring and documentation

It should be ensured that all procedures associated with the storage of tissues and cells are documented in the standard operating procedures and that storage conditions comply with specified requirements.

Continuous monitoring systems should be utilized to ensure the required environmental conditions are maintained during storage. Appropriate data should be recorded and periodically reviewed. Alarm systems should be used which are capable of alerting personnel before a critical condition is breached. It is recommended that policies and procedures be developed for the emergency transfer of tissues or cells to a designated alternative storage device or facility, and for alternative monitoring methods in the event of failure of equipment or power.

All steps during tissue or cell handling that require maintenance of a controlled temperature or other storage parameter should be documented. The documentation system should guarantee traceability of the cells or tissues.

H.7 Cross-contamination

To prevent cross-contamination, storage facilities should be dedicated. They should be physically separated from the area of procurement and/or the manufacturing area.

Notwithstanding the storage method used, separate areas should be assigned for the storage of non-tested cells and tissues (quarantine area) and tested material, ready for release. These different areas should be clearly identified.

In addition, physically separated areas should be identified and dedicated to the storage of cells or tissues that do not meet routine specifications.

Contaminated tissues and cells, e.g. those with positive biological infection markers, should be clearly and conspicuously labelled in a way that announces their particular characteristics. For example, contaminated product could be labelled with a “biological hazard” symbol (see ISO 7010). These cells are stored if necessary in suitable isolated storage enclosures in order to avoid the risk of cross-contamination or mix-ups. In the particular case of storage in a liquid nitrogen tank, these products should be stored only in vapour phase.

The vectors for the preparation of the genetic modified cells should be stored in identified and dedicated areas separate from cells and tissues.

H.8 Storage of non-cellular material

In a storage facility for cells and tissues, areas assigned to the storage of the supplies, consumables, reusable hardware (e.g. glassmaking) and ancillary products used during the tissue and cell processing should be distinct from the tissue and cell storage areas.

H.9 Storage of waste with biological risk/biohazard

Contaminated or potentially contaminated waste, generated by the processes of tissue and cell storage, should be adequately segregated fulfilling specific written requirements for the risks of infection.

H.10 Stability

Shelf life for the cells or tissues under specified storage conditions should be determined for the following materials:

a) all intermediates subject to storage, if applicable;

b) components of the combined cell-based medical product;

c) the cells or tissues;

d) the finished product.

Furthermore, a valid in-use shelf life (after opening from the transport container) should be assigned to the final product. All storage conditions, including temperature range, should be defined. Transportation and storage conditions should be supported by experimental data with regard to the maintenance of cell integrity and product stability during the defined period of validity. If relevant, appropriate methods for freezing and thawing should be documented.

Due to the complex nature of cell-based medical products, requirements for stability should be defined on a case-by-case basis. Whenever possible, stability should be assessed for both the cellular as well as the non-cellular component prior to combination, and together as a finished product in the final packaging.

H.11 Storage conditions for the final product

The potential for storage of cell- or tissue-based products is, in general, limited. However, some products may allow for storage in, for example, a frozen state. For this type of medical product, all relevant sections of this annex apply.

Annex I
(normative)

Requirements for traceability

I.1 General

A system shall be used which allows complete traceability of the starting material to the patient and vice versa, while maintaining confidentiality of patient and donor. This is essential to monitor the safety and efficacy of cell-based medical products. The establishment and maintenance of that system shall be done in a way that ensures coherence and compatibility with traceability and vigilance requirements.

I.2 Specific requirements

To guarantee the anonymity of the donor, a two-tiered system connecting the required traceability from cell donation and procurement to the manufacturer and user (hospital or practice) shall be established.

At the tissue establishment, there shall be a link between the donor and the donation. On the manufacturing side, there shall be a link between donation and product. At the hospital or practice, there shall be a link between the product and the recipient.

The systems shall allow full traceability from the donor to the recipient through anonymous coding systems. Manufacturers shall establish their coding systems in a rational way, building from the coding system of the tissue establishment and designing it to facilitate the tracing of the donation of the product to the patient. Bar coding and peeling labelling systems can be suitable tools for the purpose of patient management.

Guidance can be found in Reference [29].

The requirements for labelling are specified in F.7.

Annex J
(normative)

Risk reduction measures relating to contamination with viruses and other infectious agents such as TSE

J.1 General

In order to maintain the characteristics of cell-based medical products, living cells cannot usually be treated with physical or chemical methods that are effective for inactivation or removal of infectious agents, like viruses or the TSE agent. Until methods for inactivation or removal of infectious agents are validated, the safety of cell-based medical products depends on appropriate selection and testing of the donors and the appropriateness of raw materials used during processing. Stringent sourcing requirements and acceptance criteria for all materials derived from human origin shall be established to ensure that cells or tissues used as source material for cell-based medical products are not contaminated and that materials used for processing do not introduce infectious agents.

A single primary cell isolate may be used directly for cell-based medical products or cultured for a few passages, so that extended testing cannot be performed. An appropriate testing regime of donors should therefore be applied as it has been developed, e.g. in Europe[35] and in the USA[53]. Details are provided in Annex C. Pooling of cells can increase the risk of disease transmission. Where cell lines are used, appropriate characterized Master Cell Banks (MCB) and Working Cell Banks (WCB) should be established, whenever possible.

In the development and production of cell-based medical products, appropriate measures shall be taken to minimize the risk of virus transmission; a risk of contamination with TSEs shall be taken into account. The following aspects shall be considered.

J.2 Source of virus/TSE contamination

J.2.1 Human tissues and cells

The manufacturing process for cell-based medical products usually does not include terminal sterilization, purification steps, virus removal and/or inactivation steps. Therefore stringent sourcing requirements and acceptance criteria for all materials derived from human or animal origin according to the intended use shall be adequately defined.

Generally, human tissues and cells can harbour viruses. These are human pathogenic viruses which might grow under processing conditions, for instance during the expansion of cells. In general all blood-borne viruses shall be considered as potential contaminants. Tissue-specific viruses, such as herpes viruses (CMV, EBV) associated with blood cells, shall be considered in addition.

The risk of contamination of human tissues with the variant Creutzfeldt–Jakob disease (vCJD) agent shall be taken into consideration and, if applicable, appropriate donor selection criteria shall be applied. See References [35] and [53].

The manufacture of cell-based medical products shall be in compliance with the principles of good manufacturing practices. The manufacturing area shall be physically separated from the procurement area. If different tissues and cellular products are processed and stored in the same manufacturing area, there is an increased risk of cross-contamination during each step of the procedure, e.g. via processing equipment or in storage containers such as liquid nitrogen tanks. Therefore, adequate control measures to prevent cross-contamination shall be put into place.

Autologous cell therapy products might also be developed from virus-positive (e.g. HIV, HBV, HCV) patients. It is important to check whether viruses are amplified during *ex vivo* cell culture. In addition, a rigorous concept to avoid cross-contamination between virus-positive and virus-negative cell cultures shall be in place.

J.2.2 Processing aids

Various materials are needed for collection, selection, culture or even genetic or phenotypic modification of cells, such as other cells, enzymes, antibodies, cytokines, sera and antibiotics. Each substance used in the procedure shall be clearly specified and evaluated as to its suitability for the intended use. The quality of biologically active additives in culture media such as growth factors, cytokines and antibodies shall be documented and their quality and safety considered. Even the safety of amino acids shall be controlled. If they are derived from animal source materials, documented evidence shall be provided that there is no risk of contamination with animal TSEs.

For expansion of cells, foetal bovine serum (FBS) is frequently used. It is well known that FBS can be contaminated with viruses (see References [41], [61] and [62]). Porcine trypsin, often used in cell cultivation, bears a risk of contamination. Testing of serum or trypsin, e.g. reported by the supplier in the Certificate of Analysis (CoA), is not sufficient to assure the absence of virus contaminants; the sensitivity of the detection methods applied and the low volume that can be used for testing are the reasons for the limited value of testing. The use of these components shall be avoided, unless justified and documented. If justified, inactivated serum and/or inactivated trypsin shall be used. If human serum is used as a medium additive, the absence of virus contaminants shall be justified by appropriate measures.

When using FBS material, the manufacturer shall show

a) compliance with ISO 22442 (all parts), or

b) a Certificate of Suitability as issued by EDQM (European Directorate for the Quality of Medicines and Health Care), or equivalent.

Appropriate documentation from the supplier, demonstrating the quality and the virus and TSE safety of all human or animal derived raw materials, is needed. It is very important to consider this point early in product development and to maintain documentation of all raw materials over the different cycles of product development.

J.3 Risk reduction methods

J.3.1 Testing of donors of human tissue and cells

Specific requirements for donor selection and testing have been developed, e.g. in Europe[35] and in the USA[53]. Details are provided in Annex C. The viral infection status of any cell sample, including autologous cells, shall be known in order to permit appropriate segregation of infected cells and establish appropriate safety measures for handling and storage of cells and materials.

J.3.2 Testing of cell banks

Where cell lines are used, an appropriately characterized Master Cell Bank (MCB) and Working Cell Bank (WCB) shall be established, whenever possible. Cell banking, including cell characterization and testing, should comply with the ICH guideline Q5D[17].

J.3.3 Selection of appropriate raw materials and/or reagents

Various raw materials or reagents may be needed for collection, selection, culture and modification of cells. The quality of biological materials shall be well documented and each substance used in the procedure shall be clearly specified and evaluated according to the intended use.

The risk of contamination with adventitious agents shall be considered and, especially, all animal or human derived raw materials and/or reagents shall be implemented in the risk evaluation. The general strategy is to avoid the use of biological materials if ever possible. If this is not possible, the following considerations shall be taken into account.

For *in vitro* growth of primary cells, serum is an appropriate medium additive and many cells cannot be successfully cultivated without serum. If the use of bovine serum is considered to reduce the risk of contamination, only foetal bovine serum and, if possible, inactivated FBS products shall be used. Suppliers shall provide documented evidence that the inactivation procedure in place is effective for virus inactivation and that appropriate testing is performed before inactivation, which demonstrates, with the exception of BVDV, that the serum is free of detectable bovine viruses. Gamma irradiation at 30 kGy or higher has been shown to be effective for virus inactivation (see References [31], [36] and [40]).

If FBS is used, measures shall be taken to reduce the risk of TSE. Relevant standards, such as ISO 22442 (all parts), and guidelines, such as Reference [41], shall be considered.

The potential sensitivity of the patient, such as allergic reaction and/or antibody formation, to processing aids of animal origin shall be addressed.

It is possible to reduce the risk of contamination with bovine viruses during cultivation of cells by the use of human serum as a medium additive, but appropriate measures shall be in place to avoid contamination with human viruses. In the case of autologous cell therapy products, serum of the patient may be appropriate for use as a cell culture additive.

Trypsin is often used for cell cultivation. It can be derived from porcine tissues and can therefore be contaminated with porcine viruses, especially with porcine parvovirus and/or porcine circovirus type 1/2. Both are viruses with a high resistance to heat and chemical inactivation. Therefore, if possible, inactivated porcine trypsin, plant derived or recombinant trypsin shall be used.

Human or animal derived materials, including cells that function as support for growth and adhesion, e.g. feeder cells, shall be evaluated and/or validated as to their suitability for the intended use. If animal cells are used, they shall be tested in the absence of detectable species-specific viruses by appropriate, validated assays. Guidance documents can be consulted to select the relevant viruses for the establishment of an appropriate test regime (see References [16], [32], [54] and [55]).

When the raw materials, reagents and/or excipients have a marketing authorization or are mentioned in the Pharmacopoeia, appropriate references shall be made. If other guidance documents are applicable, such as for monoclonal antibodies[30][56] or for plasma-derived medicinal products[42], or for the virus safety assessment of biopharmaceuticals[16], they shall be taken into account. Such materials shall only be used for production of cell-based medical product if their virus/TSE safety is adequately demonstrated[41].

Annex K
(informative)

Guidance relating to hazards caused by the tumorigenic potential of human cells or tissues used for the production of medical products

The risk of inducing tumorigenesis due to neoplastic transformation of host cells and cells from cell-based medical products, should be considered, as appropriate, on a case-by-case basis. Conventional carcinogenicity studies might not be feasible. Tumorigenicity studies may be performed *in vitro* and/or *in vivo*. The decision on the tests to be performed should be made on a case-by-case basis with suitable models and on literature reviews. Tumorigenicity studies should preferably be performed with cells that are at the limit of routine cell culturing or even beyond that limit. Tissues found to contain applied cells or expressed products during the biodistribution studies should also be analysed with special emphasis during tumorigenicity studies.

Genotoxicity studies are not considered necessary for human cell-based medical products, unless the nature of any expressed product indicates an interaction directly with desoxyribonucleic acid (DNA) or other chromosomal material.