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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.