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Medical devices utilizing animal tissues and their derivatives —

Part 3: Validation of the elimination and/or inactivation of viruses and transmissible spongiform encephalopathy (TSE) agents

Dispositifs médicaux utilisant des tissus animaux et leurs dérivés — Partie 3: Validation de l'élimination et/ou de l'inactivation des virus et autres agents responsables d'encéphalopathie spongiforme transmissible (EST)

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ISO copyright office
Case postale 56 • CH-1211 Geneva 20
Tel. + 41 22 749 01 11
Fax + 41 22 749 09 47
E-mail copyright@iso.org
Web www.iso.org

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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 22442-3 was prepared by Technical Committee ISO/TC 194, *Biological evaluation of medical devices*, Subcommittee SC 1, *Tissue product safety*.

ISO 22442 consists of the following parts, under the general title *Medical devices utilizing animal tissues and their derivatives*:

— *Part 1: Application of risk management*

— *Part 2: Controls on sourcing, collection and handling*

— *Part 3: Validation of the elimination and/or inactivation of viruses and transmissible spongiform encephalopathy (TSE) agents*

Introduction

Certain medical devices utilize materials of animal origin.

Animal tissues and their derivatives are used in the design and manufacture of medical devices to provide performance characteristics that were chosen for advantages over non-animal based materials. The range and quantities of materials of animal origin in medical devices vary. These materials can comprise a major part of the device (e.g. bovine/porcine heart valves, bone substitutes for use in dental or orthopaedic applications, haemostatic devices), can be a product coating or impregnation (e.g. collagen, gelatine, heparin), or can be used in the device manufacturing process (e.g. tallow derivatives such as oleates and stearates, foetal calf serum, enzymes, culture media).

It is important to be aware that the exposure to a properly validated and accurately controlled method of viral and TSE inactivation/elimination is not the only factor associated with demonstrating product safety. Attention has also to be given to a number of factors including sourcing, collecting, handling, storage, processing, testing of tissues and/or cells of animal origin, and to the control of the environment in which the product is manufactured, assembled and packaged. The manufacturer should consider the fact that each manufacturing phase can contribute to contamination as well as elimination and/or inactivation of viruses and TSE agents.

For the safety of medical devices there are two complementary approaches (see ISO 22442-1) that can be adopted to control the potential contamination of tissues. These typically are:

a) selecting source material for minimal contamination with viruses and/or TSE agents (see ISO 22442-1 and ISO 22442-2);

b) providing valid scientific evidence to demonstrate the ability of the production processes to eliminate or inactivate viruses and/or TSE agents (this part of ISO 22442).

Requirements for a quality system for medical devices for regulatory use are specified in ISO 13485. The standards for quality management systems recognize that, for certain processes used in manufacturing, the effectiveness of that process cannot be fully verified by subsequent inspection and testing of the product. The elimination and/or inactivation of viruses and TSE agents is an example of a special process because process efficacy cannot be verified by inspection and testing of the product. For this reason, the following need to be considered in particular:

— definition of the process(es) and materials to be used;

— adequate inactivation validation before routine use;

— performance monitoring of the process during manufacture;

— appropriate equipment maintenance;

— staff training, etc.

Historically there have been many instances of unknown or unsuspected viral contamination during manufacture. For this reason, evaluation of the manufacturing process can provide a measure of confidence that a wide number of viruses, including unknown pathogenic viruses are eliminated. Similar principles may apply to TSE agents.

NOTE To show compliance with this part of ISO 22442, its specified requirements should be fulfilled. The guidance given in the Notes and informative annexes is not normative and is not provided as a checklist for auditors.

Medical devices utilizing animal tissues and their derivatives —

Part 3: Validation of the elimination and/or inactivation of viruses and transmissible spongiform encephalopathy (TSE) agents

1 Scope

This part of ISO 22442 specifies requirements for the validation of the elimination and/or inactivation of viruses and TSE agents during the manufacture of medical devices (excluding *in vitro* diagnostic medical devices) utilizing animal tissue or products derived from animal tissue, which are non-viable or have been rendered non-viable. It applies where required by the risk management process as described in ISO 22442-1. It does not cover other transmissible and non-transmissible agents.

NOTE 1 Analysis and management of risk is described in ISO 22442-1. Conventional processes used for sterilization, when used for the treatment of animal tissues for medical devices, have not been shown to be completely effective in inactivating the causative agents of transmissible spongiform encephalopathy. Selective sourcing is extremely important (see ISO 22442-1 and ISO 22442-2).

NOTE 2 ISO 11135, ISO 11137, ISO 11737-1, ISO 13408, ISO 14160, ISO 14937 and ISO 17665 may be relevant for bacteria, moulds and yeast (see Bibliography).

This part of ISO 22442 does not cover the utilization of human tissues in medical devices.

This part of ISO 22442 does not specify a quality management system for the control of all stages of production of medical devices.

NOTE 3 It is not a requirement of this part of ISO 22442 to have a full quality management system during manufacture, but it does specify requirements for some of the elements of a quality management system. Attention is drawn to the standards for quality management systems (see ISO 13485) that control all stages of production or reprocessing of medical devices. The quality management system elements that are required by this part of ISO 22442 can form part of a quality management system conforming to ISO 13485.

This part of ISO 22442 does not consider the effect of any method of elimination and/or inactivation on the suitability of the medical device for its intended use.

2 Normative references

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

ISO 22442-1:2007, *Medical devices utilizing animal tissues and their derivatives — Part 1: Application of risk management*

ISO 22442-2, *Medical devices utilizing animal tissues and their derivatives — Part 2: Controls on sourcing, collection and handling*

3 Terms and definitions

For the purposes of this document, the terms and definitions given in ISO 22442-1 and the following apply.

3.1
model TSE agent
TSE agent that displays a known resistance to physical and/or chemical processing used as reference by analogy for the inactivation of relevant TSE agents, and thereby demonstrating the effectiveness of the process used for inactivation

3.2
model virus
virus that displays a known resistance to physical and/or chemical processing used as reference by analogy for the inactivation of relevant viruses, and thereby demonstrating the effectiveness of the process used for inactivation

NOTE This includes viral models (RNA, DNA, enveloped, non-enveloped) and bacteriophage models.

3.3
overall reduction factor
sum of the reduction factors of the individual process steps

3.4
permissive cell
cell that can become infected with the virus under study and in which that virus replicates

3.5
reduction factor
ratio of the virus or TSE agent load in the relevant material used or the device prior to the inactivation or elimination step and the virus or TSE agent load after the inactivation or elimination step when it is ready for the next step in the manufacturing process, expressed as the number of ten fold reduction ($\log_{10}$)

3.6
relevant TSE agent
TSE agent known to, or likely to, contaminate the source material or other materials used in the manufacturing process

3.7
relevant virus
virus known to, or likely to, contaminate the source material or other materials used in the manufacturing process

3.8
revalidation
set of documented procedures to confirm an established validation

3.9
scaled down process
scaling down
process at a specified reduced scale which simulates the performance parameters as used in the full scale production process

3.10
sterilization
validated process used to render a product free of all forms of viable microorganisms

3.11
validation
documented procedure for obtaining, recording and interpreting the results required to establish that a process will consistently yield product complying with predetermined specifications

[ISO/TS 11139:2006, definition 2.55]

4 General requirements

4.1 Risk management

Analysis and management of risk shall be carried out in accordance with ISO 22442-1.

Due account shall be taken of manufacturing processes that are considered to be effective for certain animal materials as discussed in Annex C of ISO 22442-1:2007.

4.2 Sourcing and manufacturing process

A documented system shall be established and maintained to control the source of raw materials of animal origin. ISO 22442-2 shall be used to meet this requirement as far as applicable.

The manufacturing process shall be established to minimize the load of viruses and TSE agents in starting materials, intermediate products and finished products.

Appropriate documented protocols and procedures shall be established to ensure that the validated processing parameters will be applied during the routine manufacturing processes.

NOTE Employing a quality management system complying with ISO 13485 could be used to meet the requirements of this subclause.

4.3 General requirements related to validation

4.3.1 Documented procedures

The documented procedures and requirements of this part of ISO 22442 shall be implemented. Documentation and records shall be reviewed and approved by designated personnel (see 4.3.2).

Procedures for any literature review and/or any inactivation study shall be documented and records shall be retained for a period defined by the manufacturer.

4.3.2 Personnel

Responsibility for the implementation of this part of ISO 22442 shall be assigned to qualified personnel.

The requirements for the qualification, training or experience of personnel shall be documented and appropriate to the individual's work, responsibility and authority.

NOTE The level of qualification, training and experience required by personnel at various levels depends upon the activities being performed.

4.3.3 Calibration

An effective system shall be established, documented and maintained for the calibration of all controlling, indicating and recording instruments used for validation.

4.3.4 Equipment

Appropriate equipment as specified in a protocol shall be used. All equipment requiring planned maintenance shall be maintained in accordance with documented procedures. Records of maintenance shall be retained.

In particular, any equipment shall be capable of delivering its intended process within defined limits. In addition, if the equipment used during validation is not identical to that used in normal production cycles, adequate documentation shall be available to demonstrate that the performance parameters are equivalent to those used in the production cycle.

4.3.5 Experimental systems

Additional parts of the experimental systems used for validation studies such as chemicals, cell systems and laboratory animals shall be adequately identified, justified, controlled and documented.

5 Literature review

5.1 Conduct of the literature review

A literature review shall be performed as specified in Annex A, in order to identify and analyse data on the elimination and/or inactivation of viruses and TSE agents.

5.2 Application of literature review output

Technical information from the literature review shall be used in optimizing the design of an inactivation and/or elimination study.

Any extrapolation based on the inactivation of viruses and TSE agents shall be justified and documented.

Intrinsic variability of materials of animal origin utilized in medical devices and of manufacturing processes can lead to misinterpretation of the validity of published data and shall be taken into account.

5.3 Viruses

The manufacturer shall demonstrate whether the literature review provides an indication of which inactivation and/or elimination steps are likely to be effective. A literature review is a prerequisite to performing a viral inactivation study. In exceptional cases, if a manufacturer chooses not to perform a study, this shall be justified and documented.

If the available information does not support the elimination and/or inactivation of viruses, then an alternative risk management strategy shall be implemented (see ISO 22442-1).

5.4 TSE agents

The literature review shall consider which of the published methods for elimination and/or inactivation of TSE agents are likely to be suitable for the medical device under consideration. In particular, the materials of animal origin and manufacturing processes referred to in the literature shall be comparable to those used for the medical device under consideration (see Annex A). A validated inactivation study shall be performed when the comparability of materials and processes cannot be demonstrated or specific claims are made for inactivation of TSE agents by the manufacturer (see Clause 6).

If the available information does not support the elimination and/or inactivation of TSE agents, then an alternative risk management strategy shall be implemented (see ISO 22442-1).

Special considerations for the manufacture of some animal materials are provided in ISO 22442-1:2007, Annex C.

6 Elimination and/or inactivation study of viruses and TSE agents

6.1 General

If the need for an elimination and/or inactivation study is identified (see 5.3 and 5.4) this shall be performed so that it substantiates the effectiveness for the selected steps of manufacture against selected agents (see Annexes B and C).

If the manufacturer uses sterilization processes that have been validated for bacteria, moulds and yeast, these processes shall also be supported by relevant validation data for the elimination and/or inactivation of viruses and TSE agents.

6.2 Protocol

The protocol for a study to demonstrate the elimination and/or inactivation of viruses and TSE agents during manufacture shall detail the following including, if applicable, values and acceptability criteria:

a) the identified risks associated with the tissue concerned (see ISO 22442-1);

b) identification of the relevant agent(s);

c) the rationale for the choice of the particular combinations of model agents: the models for an elimination and/or inactivation study shall be chosen by the manufacturer; the justification for the choice of model(s) shall be documented;

NOTE 1 Such models include viral models (RNA, DNA, enveloped, non-enveloped, see also Table B.1), and TSE agent models.

NOTE 2 As part of the studies, it is possible to use bioassay of TSE agents (mouse or hamster models) for the validation of the inactivation of agents by the manufacturing process(es) of the medical device or components. Such studies have been considered to be predictive of inactivation efficacy for TSE agents which may cause disease, e.g. bovine spongiform encephalopathy, scrapie and Creutzfeldt-Jacob disease.

d) identification and definition of the manufacturing stage(s) chosen to eliminate and/or inactivate the relevant viruses and TSE agents;

e) documentation of any scaling down, including demonstration of the validity of the scaled down version of the manufacturing process;

NOTE 3 Guidance on scaling down is given in Annex D.

NOTE 4 Consideration should be given to the potential for one processing stage to have an adverse effect on the inactivation/elimination efficacy of subsequent processing stages. Reliance on literature information on individual processing stage efficacy might be inappropriate if the available information does not relate to the same sequence of processes intended for use by the manufacturer.

NOTE 5 The overall reduction factor is unlikely to equal the sum of the reduction factors from individual processing stages which use similar physical, chemical, enzymatic or thermal mechanisms or reagents to reduce the viral or TSE agent load. There may be a loss of efficacy in subsequent application of the same processing stage.

f) the methods of calculation for the reduction factors;

g) the method of the estimation of reduction kinetics, if applicable (see Annexes E and F).

NOTE 6 Careful consideration should be given to the statistical and physical limitations in sampling, and limits of sensitivity of detection methods (see also B.3.5 and Annexes C, E and F).

6.3 Conduct of the study

The study shall be conducted in accordance with the protocol.

6.4 Interpretation of data

The reduction factor shall be determined (see B.3.5 and Annexes C, E and F). The efficacy of the identified manufacturing steps for the elimination and/or inactivation of viruses and TSE agents shall be reviewed. Scaling down and other variables which may influence the results shall be addressed.

NOTE Reduction factors are typically calculated for each step within a controlled study.

7 Final report

A final report shall be compiled containing:

— the literature review (see Clause 5 and Annex A);

— and/or a critical evaluation of the data obtained during any elimination;

— and/or inactivation study undertaken (see Clause 6);

— an overall conclusion;

— reference to this part of ISO 22442.

The report shall identify manufacturing parameters that are critical to the effectiveness of the inactivation or elimination process. Acceptable limits shall be determined and specified for such parameters.

An overview shall be given showing all relevant processing steps with a statement of agent reduction factors (see B.3.5 and Annex C).

NOTE This can take the form of a flow chart.

The report shall be signed by persons designated as responsible for its preparation, review and approval. The report shall be retained and included in the risk management file [for revalidation(s), see Clause 8].

8 Review of final report

Procedures for a review of the final report by persons designated as responsible shall be documented.

A review of the final report shall be conducted when significant changes in the manufacturing process(es) occur and/or when relevant information not previously considered in the final report, becomes available, e.g. valid scientific evidence, scientific literature and authoritative publications. If necessary, corrective actions and/or additional studies shall be undertaken and reported to revalidate the manufacturing process.

Records of any review of the final report shall be retained.

9 Routine monitoring and control of critical process parameters

The manufacturer shall assure that all critical parameters identified in the final report are monitored and controlled during manufacture.