SLOVENSKI STANDARD

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Ģivalska tkiva in njihovi derivati, uporabljeni v proizvodnji medicinskih pripomoļ kov ï 3. del: Validacija pri izloļ itvi in/ali inaktivaciji virusov in nalezljivih agensov

Animal tissues and their derivatives utilized in the manufacture of medical devices - Part 3: Validation of the elimination and/or inactivation of viruses and transmissible agents

Tierische Gewebe und deren Derivate, die zur Herstellung von Medizinprodukten eingesetzt werden - Teil 3: Validierung der Abreicherung und/oder Inaktivierung von Viren und
übertragbaren Krankheitserregern

Tissus animaux et leurs dérivés utilisés dans la fabrication des dispositifs médicaux - Partie 3: Validation de l'élimination et/ou de l'inactivation des virus et autres agents transmissibles

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English version

Animal tissues and their derivatives utilized in the manufacture of medical devices - Part 3: Validation of the elimination and/or inactivation of viruses and transmissible agents

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This European Standard was approved by CEN on 20 April 2000.

CEN members are bound to comply with the CEN/CENELEC Internal Regulations which stipulate the conditions for giving this European Standard the status of a national standard without any alteration. Up-to-date lists and bibliographical references concerning such national standards may be obtained on application to the Management Centre or to any CEN member.

This European Standard exists in three official versions (English, French, German). A version in any other language made by translation under the responsibility of a CEN member into its own language and notified to the Management Centre has the same status as the official versions.

CEN members are the national standards bodies of Austria, Belgium, Czech Republic, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Italy, Luxembourg, Netherlands, Norway, Portugal, Spain, Sweden, Switzerland and United Kingdom.

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Contents **Page**

Foreword

This European Standard has been prepared by Technical Committee CEN/TC 316 "Medical devices utilizing tissues", the secretariat of which is held by IBN.

This European Standard shall be given the status of a national standard, either by publication of an identical text or by endorsement, at the latest by March 2000, and conflicting national standards shall be withdrawn at the latest by March 2000.

This European Standard has been prepared under a mandate given to CEN by the European Commission and the European Free Trade Association, and supports essential requirements of EU Directive(s).

For relationship with EU Directive(s), see informative Annex ZA, which is an integral part of this standard.

This Part of EN 12442 has been considered by CEN/TC 316 as one of a series of European Standards concerned with the development of European Standards for medical devices manufactured utilizing tissues or derivatives of animal origin, non-viable or rendered non-viable. These standards are :

EN 12442-1 Animal tissues and their derivatives utilized in the manufacture of medical devices - Part 1: Analysis and management of risk.

EN 12442-2 Animal tissues and their derivatives utilized in the manufacture of medical devices - Part 2: Controls on sourcing, collection and handling.

According to the CEN/CENELEC Internal Regulations, the national standards organizations of the following countries are bound to implement this European Standard: Austria, Belgium, Czech Republic, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Italy, Luxembourg, Netherlands, Norway, Portugal, Spain, Sweden, Switzerland and the United Kingdom.

Introduction

Certain medical devices may contain materials of animal origin.

The use of animal tissues and derivatives will give performance characteristics expected to be superior to non-animal based materials such as metal, plastics or textiles. The range and quantities of materials of animal origin in medical devices vary. These materials may comprise a major part of the device (e.g. bovine/porcine heart valves, catgut sutures, haemostatic devices), a product coating or impregnation (e.g. heparin, gelatin, collagen), or aid the manufacturing stages of production (e.g. tallow).

It is important to be aware that the exposure to a properly validated and accurately controlled method of inactivation 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 transmissible agents.

For the safety of medical devices there are two complementary approaches (see EN 12442-1) that can be adopted to control the potential contamination of tissues. These typically are:

a) selecting source material for minimal contamination with agents (see EN 12442-1 and EN12442-2);

b) testing the ability of the production processes to remove or inactivate agents (this standard, EN 12442-3).

Requirements for the quality system for the design, production, installation and servicing are given in the EN ISO 9000 and EN 46000 series of standards. These standards refer to certain manufacturing processes as 'special' if the results cannot be fully verified by subsequent inspection and testing of the product. The elimination and/or inactivation of viruses and transmissible 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.

Since many instances of contamination in the past have occurred with viruses, whose presence was not known or even suspected at the time of manufacture, an evaluation of the process can provide a measure of confidence that a wide range of viruses including unknown, harmful viruses, may be eliminated. Similar principles may apply to transmissible agents.

NOTE: To show compliance with this standard, its specified requirements should be fulfilled. The guidance given in the NOTES and informative Annexes is not obligatory and is not provided as a checklist for auditors.

1 Scope

1.1 This Part of EN 12442 specifies requirements for the validation of elimination and/or inactivation of viruses and/or transmissible agents during the manufacture of medical devices (excluding in-vitro diagnostic medical devices) utilizing materials of animal origin. It is not applicable to bacteria, moulds and yeasts.

NOTE 1: Analysis and management of risk and 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 spongiform encephalopathies. Selective sourcing is extremely important (see EN 12442-1 and EN 12442-2).

NOTE 2: EN 550, EN 552, EN 554, ISO 14160 and EN 1174 may be relevant for bacteria, moulds and yeast (see Bibliography).

1.2 This Part of EN 12442 does not cover the utilization of human tissues in medical devices.

1.3 This Part of EN 12442 does not describe a quality assurance system for the control of all stages of manufacture.

NOTE: Attention is drawn to the standards for quality systems (e.g. EN ISO 9001 and EN 46001 or EN ISO 9002 and EN 46002, see Bibliography) which may be used to control all stages of manufacture. It is not a requirement of this standard to apply a complete quality system during manufacture but certain elements of such a system are required and these are addressed at appropriate places in the text.

1.4 This Part of EN 12442 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

This European standard incorporates by dated or undated reference, provisions from other publications. These normative references are cited at the appropriate places in the text and the publications are listed hereafter. For dated references, subsequent amendments to or revisions of any of these publications apply to this European standard only when incorporated in it by amendment or revision. For undated references the latest edition of the publication referred to applies.

EN 12442-1 Animal tissues and their derivatives utilized in the manufacture of medical devices - Part 1: Analysis and management of risk

NOTE: The Bibliography lists informative references. These informative references are cited at the appropriate places in the text.

3 Terms and definitions

For the purposes of this Standard, the following terms and definitions apply.

3.1
animal
all vertebrates including fish, amphibians, reptiles, birds and mammals, excluding humans (*Homo sapiens*) [EN 12442-1 and EN 12442-2].

3.2
elimination/removal
process by which the number of viruses and transmissible agents is reduced [EN 12442-1].

NOTE 1: The effectiveness of the process should be expressed mathematically in terms of a reduction factor (See Annex E).

NOTE 2: Elimination/removal aims to prevent infection or pathogenic reaction caused by viruses and/or transmissible agents.

3.3
inactivation
process by which the ability to cause infection or pathogenic reaction by viruses and/or transmissible agents is reduced [EN 12442-1 and EN 12442-2].

NOTE 1: The effectiveness of the process should be expressed mathematically in terms of a reduction factor (see Annex E).

NOTE 2: Inactivation aims to prevent infection and replication of viruses and transmissible agents.

3.4
medical device
any instrument, apparatus, appliance, material or other article, wether used alone or in combination, including the software necessary for its proper application intended by the manufacturer to be used for human beings for the purpose of:
- diagnosis, prevention, monitoring, treatment or alleviation of disease,
- diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap,
- investigation, replacement or modification of the anatomy or of a physiological process,
- control of conception,

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

NOTE: This definition is identical with that given in Council Directive 93/42/EEC.

3.5
model agent
virus or transmissible agent which displays a known resistance to physical and/or chemical processing used as reference by analogy for the inactivation of relevant agents, and thereby demonstrating the effectiveness of the process used for inactivation.

NOTE: Such models include viral models (RNA, DNA, enveloped, non-enveloped), bacteriophage models and transmissible agent models.

3.6
overall reduction factor
sum of the reduction factors of the individual steps.

3.7
permissive cell
tissue culture cell that can become infected with the virus under study and in which that virus replicates.

NOTE: There are no known tissue culture systems for transmissible agents.

3.8
reduction factor
ratio of the virus and transmissible agent load in the device prior to the inactivation and /or elimination step and the virus and transmissible agent load after the inactivation and/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}.).

3.9
relevant agent
virus or transmissible agent known to or likely to contaminate the source material or other materials used in the manufacturing process.

3.10
revalidation
set of documented procedures to confirm an established validation.

3.11
scaled down process /scaling down
process at a specified reduced scale which simulates the performance parameters as used in the full scale production process.

3.12
tissue
organization of cells and/or extra-cellular constituents [EN 12442-1 and EN 12442-2].

3.13
transmissible agents
unclassified pathogenic entities, prions and similar entities [EN 12442-1].

NOTE: e.g. BSE agent, scrapie agent.

3.14
validation
documented procedure for obtaining, recording and interpreting the data required to show that a process will consistently comply with predetermined specifications.

4 General requirements

4.1 Sourcing and manufacturing process

A documented system shall be established and maintained to control the source of raw materials of animal origin.

NOTE 1: EN 12442-2 should be used to meet this requirement when practicable, to control the source of raw materials of animal origin.

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

Appropriate documented procedures shall be applied to ensure that the validated processing parameters are applied during routine manufacture.

NOTE 2: Employing a quality system complying with EN ISO 9001 and EN 46001 or EN ISO 9002 and EN 46002 (see Bibliography) should be used to meet the requirements of this clause.

4.2 General requirements related to validation

4.2.1 Documented procedures

The documented procedures and requirements of this standard shall be implemented. Documentation and records shall be reviewed and approved by designated personnel (see 4.2.2).

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

4.2.2 Personnel

Responsibility for the implementation of this Part of EN 12442 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 will depend upon the activities being performed. General guidance on training as part of the overall system of quality assurance is given in EN ISO 9004 (see Bibliography).

4.2.3 Calibration

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

4.2.4 Equipment

Appropriate equipment as specified in the 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 is not identical with 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.

4.2.5 Ancillaries

Ancillaries used for validation studies such as chemicals, cell systems and laboratory animals shall be adequately justified, controlled and documented.