INTERNATIONAL STANDARD

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Sterilization of medical devices — Low temperature steam and formaldehyde — Requirements for development, validation and routine control of a sterilization process for medical devices

Stérilisation des dispositifs médicaux — Formaldéhyde et vapeur à faible température — Exigences pour le développement, la validation et le contrôle de routine d'un procédé de stérilisation pour dispositifs médicaux

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Foreword

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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 25424 was prepared by CEN (as EN 15424:2007) and is submitted for approval under a special “fast-track procedure”, by Technical Committee ISO/TC 198, *Sterilization of health care products*, in parallel with its approval by the ISO member bodies.

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For the purposes of this International Standard, the CEN annex regarding the fulfilment of European Council Directives has been removed.

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Foreword

This document (EN 15424:2007) has been prepared by Technical Committee CEN/TC 204 “Sterilization of medical devices”, the secretariat of which is held by BSI.

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of an identical text or by endorsement, at the latest by October 2007, and conflicting national standards shall be withdrawn at the latest by October 2007.

This document 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).

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

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Introduction

A sterile medical device is one which is free of viable microorganisms. European Standards, which specify requirements for validation and routine control of a sterilization process require, when it is necessary to supply a sterile medical device, that adventitious microbiological contamination of a medical device prior to sterilization be minimized. Even so, medical devices produced under standard manufacturing conditions in accordance with the requirements for quality management systems (see EN ISO 13485) or which have been subjected to a cleaning process as part of their reprocessing in a health care establishment may, prior to sterilization, have microorganisms on them, albeit in low numbers. Such products are non-sterile. The purpose of sterilization is to inactivate the microbiological contaminants and thereby transform the non-sterile products into sterile ones.

The kinetics of inactivation of a pure culture of microorganisms by physical and/or chemical agents used to sterilize medical devices can generally best be described by an exponential relationship between the numbers of microorganisms surviving and the extent of treatment with the sterilizing agent; inevitably this means that there is always a finite probability that a microorganism may survive regardless of the extent of treatment applied. For a given treatment, the probability of survival is determined by the number and resistance of microorganisms and by the environment in which the organisms exist during treatment. It follows that the sterility of any one product in a population subjected to sterilization cannot be guaranteed and the sterility of a processed population is defined in terms of the probability of there being a viable microorganism present on a product item.

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This standard describes requirements which will enable the demonstration that a low temperature steam and formaldehyde sterilization process intended to sterilize medical devices has appropriate microbicidal activity, and that this activity is both reliable and reproducible, such that the relationship for the inactivation of microorganisms can be extrapolated with reasonable confidence to low levels of probability of there being a viable microorganism present on a product after sterilization. This standard does not specify the maximal value to be taken by this probability; specification of this probability is given in EN 556-1.

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Requirements of the quality management system for medical device design/development, production, installation and servicing are given in EN ISO 13485. The standard for quality management systems recognizes that, for certain processes used in manufacturing or reprocessing, the effectiveness cannot be fully verified by subsequent inspection and testing of the product. Sterilization is an example of such a process. For this reason, sterilization processes are validated for use, the performance of the sterilization process monitored routinely and the equipment maintained.

Exposure to a properly validated, accurately controlled sterilization process is not the only factor associated with the provision of reliable assurance that the product is sterile and, in this regard, suitable for its intended use. Attention is therefore given to a number of factors including:

a) the microbiological status of incoming raw materials and/or components,

b) the validation and routine control of any cleaning and disinfection procedures used on the product,

c) the control of the environment in which the product is manufactured, assembled and packaged,

d) the control of equipment and processes,

e) the control of personnel and their hygiene,

f) the manner and materials in which the product is packaged, and,

g) the conditions under which the product is transported and stored.

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The type of contamination on a product to be sterilized varies and this impacts upon the effectiveness of a sterilization process. Products that have been used in a health care setting and are being presented for re-sterilization in accordance with the manufacturer's instructions (see EN ISO 17664) should be regarded as a special case. There is the potential for such products to possess a wide range of contaminating microorganisms and residual inorganic and/or organic contamination in spite of the application of a cleaning process. Hence, particular attention has to be given to the validation and control of the cleaning and disinfection processes used during reprocessing.

The requirements are the normative parts of this standard with which compliance is claimed. The guidance given in the informative annexes is not normative and is not provided as a checklist for auditors. The guidance provides explanations as well as methods that are accepted as being suitable means for complying with the requirements. Approaches other than those given in the guidance may be used, if they are effective in achieving compliance with the requirements of this European Standard.

The development, validation and routine control of a sterilization process comprise a number of discrete but interrelated activities, for example calibration, maintenance, product definition, process definition, installation qualification, operational qualification, and performance qualification. While the activities required by this standard have been grouped together and are presented in a particular order, this European Standard does not require that the activities be performed in the order that they are presented. The activities required are not necessarily sequential, as the programs of development and validation may be iterative. It is possible that performing these different activities will involve a number of separate individuals and/or organizations, each of whom undertake one or more of these activities. This European Standard does not specify the particular individuals or organizations to carry out the activities.

Activities required by this standard might also give rise to an environmental burden that should be considered and minimized, e.g. by utilizing flexibility in planning. Environmental aspects are addressed in Annex D of this standard.

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Sterilization of medical devices — Low temperature steam and formaldehyde — Requirements for development, validation and routine control of a sterilization process for medical devices

1 Scope

1.1 Inclusions

1.1.1 This European Standard specifies requirements for the development, validation and routine control of a Low Temperature Steam and Formaldehyde (LTSF) sterilization process for medical devices.

NOTE Although the scope of this standard is limited to medical devices, it specifies requirements and provides guidance that may be applicable to other products and equipment.

1.1.2 This European Standard is intended to be applied by process developers, manufacturers of sterilization equipment, manufacturers of medical devices to be sterilized and the organizations with responsibility for sterilizing medical devices. (See EN ISO 14937:2000, Table E.1)

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1.1.3 This European Standard covers sterilization processes which use a mixture of low temperature steam and formaldehyde as sterilant, and which are working below ambient pressure only.

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1.2 Exclusions

1.2.1 Sterilization processes validated and controlled in accordance with the requirements of this standard should not be assumed to be effective in inactivating the causative agents of spongiform encephalopathies such as scrapie, bovine spongiform encephalopathy and Creutzfeld-Jakob disease. Specific recommendations have been produced in particular countries for the processing of materials potentially contaminated with these agents.

1.2.2 This standard does not specify requirements for designating a medical device as “STERILE”. Such requirements are given in EN 556-1.

1.2.3 This standard does not specify a quality management system for the control of all stages of production of medical devices.

NOTE It is not a requirement of this standard to have a complete quality management system during manufacture or reprocessing, but those elements of such a system that are required are normatively referenced at appropriate places in the text. Attention is drawn to the standards for quality management systems (see EN ISO 13485) that control all stages of production or reprocessing of medical devices including the sterilization process. Further guidance is given in E.2 of EN ISO 14937:2000.

1.2.4 This standard does not specify requirements for occupational safety associated with the design and operation of LTSF sterilization facilities.

NOTE 1 Safety requirements for sterilizers are specified in EN 61010-2-040.

NOTE 2 Attention is also drawn to the existence in some countries of regulations stipulating safety requirements.

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1.2.5 This European Standard does not cover analytical methods for determining levels or residues of formaldehyde and/or its reaction products.

NOTE 1 Attention is drawn to EN 14180.

NOTE 2 Attention is drawn to the possible existence in some countries of statutory regulation specifying limits for the level of formaldehyde residues on medical devices and products.

1.2.6 This European Standard does not cover preparatory measures that may be necessary before sterilization such as cleaning, disinfection and packing.

NOTE For re-sterilizable medical devices, the manufacturer(s) of these devices should supply information on the preparatory measures (see EN ISO 17664).

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.

EN 14180:2003, *Sterilizers for medical purposes — Low temperature steam and formaldehyde sterilizers — Requirements and testing*

EN ISO 11138-1, *Sterilization of health care products — Biological indicators — Part 1: General requirements (ISO 11138-1:2006)*

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EN ISO 11138-5:2006, *Sterilization of health care products — Biological indicators — Part 5: Biological indicators for low-temperature steam and formaldehyde sterilization processes (ISO 11138-5:2006)*

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EN ISO 11140, *Sterilization of health care products — Chemical indicators* (Parts as appropriate)

EN ISO 11737-1, *Sterilization of medical devices — Microbiological methods — Part 1: Determination of a population of microorganisms on products (ISO 11737-1:2006)*

EN ISO 11737-2, *Sterilization of medical devices — Microbiological methods — Part 2: Tests of sterility performed in the validation of a sterilization process (ISO 11737-2:1998)*

EN ISO 13485, *Medical devices — Quality management systems — Requirements for regulatory purposes (ISO 13485:2003)*

3 Terms and definitions

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

3.1
adjustment
correction of a measurement device or system to indicate the value as established by calibration

3.2
aeration
part or parts of the sterilization process in which defined conditions are used such that formaldehyde and its reaction products are desorbed from the medical device, and which can be performed within the sterilizer, within a separate room or chamber, or by a combination of the two

[3.3 of EN 14180:2003]

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3.3
air removal
removal of air from the sterilizer chamber and sterilization load to facilitate sterilant penetration

[3.3 of EN 14180:2003]

3.4
bioburden
population of viable microorganisms on or in product and/or sterile barrier system

[2.2 of ISO/TS 11139:2006]

3.5
biological indicator (BI)
test system containing viable microorganisms inoculated onto a carrier and contained within a primary pack, ready for use and providing defined resistance to a specified sterilization process under defined reference conditions

3.6
calibration
set of operations that establish, under specified conditions, the relationship between values indicated by a measuring instrument or measuring system, or values represented by a material measure or a reference material, and the corresponding values realized by standards

[2.4 of ISO/TS 11139:2006]

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3.7
change control
assessment and determination of the appropriateness of a proposed alteration to product or procedure

[2.5 of ISO/TS 11139:2006]

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3.8
chemical indicator
test system that reveals change in one or more predefined process variables based on a chemical or physical change resulting from exposure to a process

[2.6 of ISO/TS 11139:2006]

3.9
conditioning
treatment of product within the sterilization cycle, but prior to the holding time, to attain a predetermined temperature and humidity throughout the sterilization load

[3.7 of EN 14180:2003]

3.10
desorption
removal of the sterilant from the chamber and the load at the end of the exposure time

[3.11 of EN 14180:2003]

3.11
***D* value**
time or dose required to achieve inactivation of 90 % of a population of the test microorganism under stated conditions

[2.11 of ISO/TS 11139:2006]

NOTE For LTSF sterilization the D value is given in minutes.

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3.12
environmental control
engineering and/or procedural systems to maintain conditions in defined areas within specified limits

NOTE Such systems may include air and fluid filters, surface disinfection, personnel attire and administrative procedures [2.16 of ISO/TS 11139:2006].

3.13
equilibration time
period which elapses between the attainment of the sterilization temperature at the reference measuring point and the attainment of the sterilization temperature at all points within the load

[3.13 of EN 14180:2003]

3.14
establish
determine by theoretical evaluation and confirm by experimentation

[2.17 of ISO/TS 11139:2006]

3.15
exposure time
time between introducing the sterilant into the chamber and start of the desorption phase

[3.14 of EN 14180:2003]

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3.16
fault
one or more of the process parameters which lies outside of its/their specified tolerance(s)

[2.19 of ISO/TS 11139:2006]

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3.17
F_{BIO} value
product of the logarithm of the initial population of microorganisms and the D value

NOTE The F_{BIO} value may be used to express the “total resistance” of the biological indicator.

3.18
holding time
period for which the temperature, the steam pressure and the formaldehyde concentration of steam are held within pre-set values and their tolerances to achieve the required inactivation efficacy in the sterilizer chamber

NOTE The holding time follows immediately after the equilibration time [3.15 of EN 14180:2003].

3.19
inoculated carrier
supporting material on or in which a defined number of test microorganisms have been deposited

3.20
installation qualification [IQ]
process of obtaining and documenting evidence that equipment has been provided and installed in accordance with its specification

[2.22 of ISO/TS 11139:2006]

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3.21
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 purpose(s) of:

— diagnosis, prevention, monitoring, treatment or alleviation of disease,

— diagnosis, monitoring, treatment, alleviation of or compensation for an injury,

— investigation, replacement, modification, or support of the anatomy or of a physiological process,

— supporting or sustaining life,

— control of conception,

— disinfection of medical devices,

— 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 function by such means

[EN ISO 13485]

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3.22
microbicidal solution
aqueous solution containing formaldehyde to feed the vaporizer for generating sterilant in the sterilizer

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[3.20 of EN 14180:2003]

NOTE The microbicidal solution usually contains stabilizers i.e. alcohols.

3.23
operational qualification (OQ)
process of obtaining and documenting evidence that installed equipment operates within predetermined limits when used in accordance with its operational procedures

[2.27 of ISO/TS 11139:2006]

3.24
parametric release
declaration that a product is sterile, based on records demonstrating that the process parameters were delivered within specified tolerances

[2.29 of ISO/TS 11139:2006]

3.25
performance qualification (PQ)
process of obtaining and documenting evidence that the equipment, as installed and operated in accordance with operational procedures, consistently performs in accordance with pre-determined criteria and thereby yields product meeting its specification

[2.30 of ISO/TS 11139:2006]

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