SLOVENSKI STANDARD

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Sterilizacija medicinskih pripomoļ kov ï Aseptiļ na proizvodnja tekoļ ih medicinskih pripomoļ kov - Zahteve

Sterilization of medical devices - Aseptic processing of liquid medical devices - Requirements

Sterilisation von Medizinprodukten - Aseptische Herstellung flüssiger Medizinprodukte - Anforderungen

Stérilisation des dispositifs médicaux - Traitement aseptique des dispositifs médicaux liquides - Exigences

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This European Standard was approved by CEN on 14 October 2004.

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Foreword

This document (EN 13824:2004) 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of an identical text or by endorsement, at the latest by May 2005, and conflicting national standards shall be withdrawn at the latest by May 2005.

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).

For relationship with EU Directive(s), see informative Annexes ZA and ZB, which are integral parts of this document.

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Introduction

Medical devices that are labelled ‘sterile’ have to be prepared using appropriate and validated methods. CEN TC 204 has prepared standards relating to terminal sterilization of medical devices by irradiation (EN 552), by moist heat (EN 554), by liquid chemical sterilants (EN ISO 14160) and by ethylene oxide (EN 550). When a medical device is intended to be sterile and cannot be terminally sterilized, aseptic processing provides an alternative method.

Aseptic processing requires the application of validated sterilization processes to all equipment components that come into contact with the aseptically processed material prior to the use of that equipment. This is also necessary for container components. The sterilized equipment and container components are then assembled in a manner that maintains their sterility. The product is processed in a controlled environment where microbial and particulate levels are maintained at defined levels and where human intervention is minimized.

Sterilization practice is an exacting and demanding discipline. Manufacturers require validated systems, adequately trained personnel, controlled environments and well-documented systematic processes to ensure a sterile product. The application of this to aseptic processing is discussed below.

While terminal sterilization involves the use of a process of known lethality, the assurance of sterility associated with aseptic processing can only be inferred, as facilities, equipment and people are all factors associated with the process and its control. Issues that need particular attention for aseptic processing include:

a) personnel;

b) layout and specifications for buildings, equipment and facilities;

c) particulate and microbial environmental monitoring programmes;

d) the satisfactory function of validated systems for production of water, steam and other process gases of appropriate quality;

e) descriptions of and procedures for manufacturing operations including people, materials, material flow, solution preparation and associated acceptance criteria;

f) validation and routine control of cleaning, disinfection and sterilization processes;

g) validation methods and data requirements for media fills and container/closure systems and

h) operating practices for acceptance criteria, investigation reviews and release/reject decisions.

1 Scope

This document specifies requirements for the design and operation of aseptic processing facilities and the validation and routine control of aseptic processes for the preparation of sterile liquid medical devices. It is not applicable to those pharmaceutical products where the requirements of the relevant good manufacturing practices are applicable.

NOTE Many of the principles included in this document can be applied to certain aseptically processed sterile solid medical devices.

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 980, *Graphical symbols for use in the labelling of medical devices.*

EN 1174-1, *Sterilization of medical devices — Estimation of the population of micro-organisms on product — Part 1: Requirements.*

EN 1174-2, *Sterilization of medical devices — Estimation of the population of micro-organisms on product — Part 2: Guidance.*

EN 1174-3, *Sterilization of medical devices — Estimation of the population of micro-organisms on product - Part 3: Guide to the methods for validation of microbiological techniques.*

EN 1822-1:1998, *High efficiency air filters (HEPA and ULPA) — Part 1: Classification, performance testing, marking*.

EN 1822-2:1998, *High efficiency air filters (HEPA and ULPA) — Part 2: Aerosol production, measuring equipment, particle-counting statistics.*

EN ISO 14644-1:1999, *Cleanrooms and associated controlled environments — Part 1: Classification of air cleanliness (ISO 14644-1:1999).*

EN ISO 14644-2:2000, *Cleanrooms and associated controlled environments — Part 2: Specifications for testing and monitoring to prove continued compliance with ISO 14644-1 (ISO 14644-2:2000).*

prEN ISO 14644-3:2002, *Cleanrooms and associated controlled environments — Part 3: Metrology and test methods (ISO/DIS 14644-3:2002).*

EN ISO 14644-4:2001, *Cleanrooms and associated controlled environments — Part 4: Design, construction and start up (ISO 14644-1:2001).*

prEN ISO 14644-7:2001, *Cleanrooms and associated controlled environments — Part 7: Separative enclosures (clean air hoods, gloveboxes, isolators, minienvironments) (ISO 14644-7:2004).*

European Pharmacopoeia: monographs for Purified Water and Water for Injections. European Department for the Quality of Medicines

European Pharmacopoeia: Test for sterility. European Department for the Quality of Medicines

Rules governing medicinal products in the European Union, Volume 4, Guide to Good Pharmaceutical Manufacturing Practices, Commission of European Communities, Brussels/Luxembourg (current edition available from http://pharmacos.eudra.org/F2/eudralex/vol-4/home.htm.

3 Terms and definitions

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

3.1
action level
(environmental monitoring)
established microbial or particulate levels requiring immediate follow-up and corrective action if exceeded

3.2
action level
(media fill)
number of positive media fill units that, if exceeded, requires immediate investigation of the cause and corrective action

3.3
alert level
(environmental monitoring)
established microbial or particulate levels giving early warning of potential drift from normal operating conditions which are not necessarily grounds for definitive corrective action but which could require follow-up investigation

3.4
alert level
(media fill)
number of positive media fill units that, if exceeded, requires immediate investigation of the cause, but that are not necessarily grounds for definitive corrective action

3.5
aseptic filling
part of aseptic processing where a pre-sterilized product, or a solution passed through a product sterilizing filter, is filled and/or packaged into sterile containers that are then closed

3.6
aseptic filling line
manufacturing structure or arrangement where containers are aseptically-filled with the liquid medical device

3.7
aseptic processing
handling and filling of sterile containers and devices, or their components, in a controlled environment in which the air supply, materials, equipment and personnel are regulated to control microbial and particulate contamination to acceptable levels

NOTE Aseptic processing can include formulation (compounding), filtration and filling into pre-sterilized containers.

3.8
aseptic processing area
(APA)
controlled environment for handling the aseptic filling of containers with liquid medical devices in which the air supply, materials, equipment and personnel are regulated to control and minimize/remove any potential risk of microbial/ particulate contamination to within pre-determined levels

3.9
batch
defined quantity of starting material, packaging material or product processed in one process or series of processes so that it could be expected to be homogeneous

3.10
batch manufacturing record
process documentation that supports the manufacturing of a batch of product consistent with defined product manufacturing and quality assurance specifications

3.11
bioburden
population of viable microorganisms in/on a product and/or package

3.12
biological indicator
microbiological test system providing a defined resistance to a specified sterilization process

3.13
cleanroom
room in which the concentration of airborne particles is controlled, and which is constructed and used in a manner to minimize the introduction, generation, and retention of particles inside the room, and in which other relevant parameters, e.g. temperature, humidity and pressure, are controlled as necessary

3.14
container configuration
identical container design independent of capacity

3.15
critical processing zone
location within aseptic processing area in which product and product contact surfaces are exposed to the environment

NOTE Aseptic manipulations performed can include aseptic connections, filling, stoppering and closing operations.

3.16
critical surface
surface within the critical processing zone in close proximity to aseptic operations and which poses a potential risk to the product

3.17
differential air pressure
difference in static pressure between rooms or enclosed spaces of different cleanliness classification

3.18
disinfectant
chemical or physical agent that inactivates vegetative microorganisms but not necessarily highly resistant spores

3.19
environmental flora
isolate
microorganisms present in and/or isolated from processing or manufacturing environments

3.20
gas filter
porous material placed in compressed gas lines to remove non-viable particulate matter and microorganisms from gas streams which come directly or indirectly in contact with a product

3.21
high efficiency particulate air filter
HEPA filter
retentive matrix complying with the specification H 14 of EN 1822-1:1998 as determined by the method described in EN 1822-2:1998 using a suitable liquid particle test aerosol

3.22
isolator
separative device creating an enclosed classified environment of minimum size in which a process or activity can be placed with a high degree of assurance that effective separation will be maintained between the enclosed environment, its surroundings, and any person involved with the process or manipulation

NOTE Isolators can be of closed or open design, and may be maintained at positive or negative pressure relative to their surroundings.

3.23
media fill
simulation of an aseptic process in which a microbial growth medium is used to assess the effectiveness of the controls applied

NOTE Media fills are synonymous with process simulation tests, simulated process fills, simulated filling operations, broth trials, broth fills.

3.24
other processing zone
processing zone, other than critical processing zones, in which medical devices are not exposed to the environment

NOTE These zones include staging, transport, and storage areas for sterilized components, containers and bulk products in protected vessels; autoclave unloading areas; and processing rooms from which critical areas are accessed.

3.25
product contact surface
surface that comes into contact with sterilized product or containers/closures

3.26
product sterilizing filter
porous material with a nominal rating of less than or equal to 0,22 µm, capable of retaining a defined number of microorganisms using defined challenge tests and conditions

3.27
qualification
action of proving that any equipment and/or process works correctly and actually leads to the expected results

NOTE The word “validation” is sometimes widened to incorporate the concept of qualification. Qualification of equipment and/or processes generally includes installation qualification, operational qualification, and performance qualification.

- *Installation qualification* - demonstrates that the unit or process under test is in compliance with all relevant design criteria and safety standards, and is calibrated.
- *Operational qualification* - testing demonstrates that the equipment and/or process functions as intended, that procedures exist describing operation of the equipment, and that personnel have been trained to set-up, operate and maintain the equipment.
- *Performance qualification* - testing involves actual challenges to the system to substantiate its effectiveness and reproducibility.

3.28
shift
scheduled period of work or production staffed by a single defined group of workers

3.29
sterile
condition of a medical device that is free from viable microorganisms

3.30
sterilization
validated process used to render a product, surface or material free from viable microorganisms

NOTE The number of microorganisms that survive a sterilization process can be expressed in terms of probability. While the probability can be reduced to a very low number, it can never be reduced to zero.

3.31
support area outside the APA
environmentally controlled area not within the aseptic processing area and not part of critical or other processing zones

3.32
terminal sterilization
process whereby a product is sterilized in its final container and which permits the measurement and evaluation of quantifiable microbial lethality

3.33
transfer device
mechanism to effect movement of material into or out of separative enclosures while minimizing ingress or egress of unwanted matter

3.34
unidirectional air flow
controlled air flow through the entire cross section of an aseptic processing area or critical processing zone with a steady velocity and approximately parallel streamlines

NOTE This type of airflow results in a directed transport of particles from the clean zone.

3.35
validation

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

3.36
vent filter
porous material capable of removing non-viable particles and microorganisms from gases passing in and out of a closed vessel

4 Quality management systems

A documented quality management system shall be established and maintained to control activities affecting aseptic processing.

NOTE 1 Guidance on the application of quality systems for medical devices is included in EN ISO 13485.

NOTE 2 The quality management system should normally include, in addition to the product, components and process specifications, written procedures and specifications for:

a) environmental conditions in the aseptic processing area (APA);

b) cleaning and disinfection of the APA;

c) sterilization of the product, equipment, and container/closure system;

d) aseptic processing of bulk products, e.g., freeze-drying, aseptic crystallization, powder drying, etc.;

e) introduction of items into the aseptic processing area or critical processing zone;

f) employee gowning practices;

g) in-process testing and evaluation;

h) operator and technician training;

i) change control practices and;

j) validation.

5 Personnel

5.1 Personnel management

5.1.1 Documented procedures for aseptic processing, personnel training and assessment of personnel performance against defined criteria, shall be established and implemented by the manufacturer.

5.1.2 The effectiveness of the documented procedures shall be evaluated at stated intervals defined by the manufacturer.

5.1.3 Training requirements for the qualification of individuals for access to the APA shall be defined and documented by the manufacturer (see 5.2).

5.1.4 Aseptic processing shall be supervised by staff trained according to criteria defined, established and implemented by the manufacturer.

NOTE Supervision of aseptic procedures should take place close to the operations concerned and at a frequency defined by the manufacturer. In case of failure to follow appropriate procedures corrective action should be taken, which can include retraining.

5.2 Training for APA qualification

5.2.1 Personnel entering the APA shall be qualified and have successfully completed training, as described in 5.2.2 and 5.2.3, consistent and in accord with their individual duties and at an appropriate level of knowledge according to criteria defined, established and implemented by the manufacturer.

5.2.2 Personnel working in the APA, including supervisors and maintenance staff, shall be trained in:

a) manufacture of sterile products within the APA;

b) fundamentals of microbiology;

c) personal hygiene;

NOTE 1 This should include hand washing and disinfection procedures.

d) rules concerning the wearing of cosmetics or jewellery;

e) aseptic technique;

NOTE 2 Training should include information relevant to employees working in the APA such as avoiding:

i) unnecessary movement and contact with critical surfaces;

ii) unnecessary movements and talking which can generate particles or create turbulence;

iii) reaching across open containers and exposed product and components and

iv) blocking air flow over critical surfaces.

f) gowning procedures;

g) emergency procedures to protect product quality.

NOTE 3 This should include contingencies such as loss of the air conditioning system, loss of power, etc.

5.2.3 Other personnel, including management and other QA/QC personnel, who require temporary access to the APA shall be accompanied at all times by a person trained and qualified in accordance with 5.2.2 and shall be trained in the essential elements of:

a) fundamentals of microbiology and

b) essential elements of aseptic technique;

c) personal hygiene;

d) rules concerning the wearing of cosmetics or jewellery;

e) gowning procedures.

5.2.4 Records of personnel training and evaluation shall be maintained.

5.2.5 Personnel that are directly involved in the filling or manufacture of sterile products in the critical processing zone shall participate in at least one successful media fill each year. (see Clause 11 and Annex E.)

5.2.6 New personnel working in the critical processing zone shall take part in at least one successful media fill before being permitted to participate in processes carried out in critical process zones. Alternatively, new personnel shall have completed a defined programme of training covering essential aseptic operations which can be performed in a training environment before being permitted to participate in processes carried out in critical process zones.

5.2.7 All personnel working in the critical processing zone shall be retrained, in accordance with procedures established and documented by the manufacturer, on both specific job functions and relevant quality systems elements, at a defined frequency, or if the manufacturer identifies a deficiency in the person's performance.

5.3 General employee health

5.3.1 Personnel shall be required to report conditions which can affect aseptic processing such as fever, skin lesions, common cold, diarrhoea, etc.

5.3.2 Personnel with reported health conditions affecting aseptic work shall not be permitted to enter the critical processing zones, but can be assigned work in other areas.

NOTE Initial and periodic medical examinations should be performed for individuals assigned to aseptic processing operations.

5.4 Monitoring of personnel

5.4.1 A microbiological monitoring programme shall be defined and documented for employees qualified to work in the APA. This programme shall include the monitoring of items such as garments and gloves.

5.4.2 Results of the monitoring programme shall be used to identify trends and evaluate the need for retraining.