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Sterilisering av medicintekniska produkter – Aseptisk hantering av vätskeformiga medicintekniska produkter – Krav

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

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English version

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

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

Sterilisation von Medizinprodukten - Aseptische Herstellung flüssiger Medizinprodukte - Anforderungen

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of an identical text or by endorsement, at the latest by May 2005, and conflicting national standards shall be withdrawn at the latest by May 2005.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