SVENSK STANDARD
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Aseptisk behandling av medicintekniska produkter – Del 4: Rengöring på plats (ISO 13408-4:2005)

Aseptic processing of health care products – Part 4: Clean-in-place technologies (ISO 13408-4:2005)

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Europastandarden EN ISO 13408-4:2011 gäller som svensk standard. Detta dokument innehåller den officiella engelska versionen av EN ISO 13408-4:2011.

Denna standard ersätter SS-EN 13824:2005, utgåva 1.

The European Standard EN ISO 13408-4:2011 has the status of a Swedish Standard. This document contains the official version of EN ISO 13408-4:2011.

This standard supersedes the Swedish Standard SS-EN 13824:2005, edition 1.

Förhållandet till övriga delar under samma huvudtitel - Utdrag ur Förord i ISO 13408-4:2011/ Relations to other parts under the same general title - Extract from the Foreword of ISO 13408-4:2011

ISO 13408 consists of the following parts, under the general title *Aseptic processing of health care products:*

- *Part 1: General requirements*
- *Part 2: Filtration*
- *Part 3: Lyophilization*
- *Part 4: Clean-in-place technologies*
- *Part 5: Sterilization in place*
- *Part 6: Isolator systems*

Upplysningar om sakinnehållet i standarden lämnas av SIS, Swedish Standards Institute, telefon 08-555 520 00. Standarder kan beställas hos SIS Förlag AB som även lämnar allmänna upplysningar om svensk och utländsk standard.

Information about the content of the standard is available from the Swedish Standards Institute (SIS), telephone +46 8 555 520 00. Standards may be ordered from SIS Förlag AB, who can also provide general information about Swedish and foreign standards.

Denna standard är framtagen av kommittén för Sterilisering av medicintekniska produkter, SIS/TK 349.

Har du synpunkter på innehållet i den här standarden, vill du delta i ett kommande revideringsarbete eller vara med och ta fram andra standarder inom området? Gå in på www.sis.se - där hittar du mer information.

EUROPEAN STANDARD

NORME EUROPÉENNE

EUROPÄISCHE NORM

EN ISO 13408-4

June 2011

ICS 11.080.01

Supersedes EN 13824:2004

English Version

Aseptic processing of health care products - Part 4: Clean-in-place technologies (ISO 13408-4:2005)

Traitement aseptique des produits de santé - Partie 4: Technologies de nettoyage sur place (ISO 13408-4:2005)

Aseptische Herstellung von Produkten für die Gesundheitsfürsorge - Teil 4: Reinigung vor Ort (ISO 13408-4:2005)

This European Standard was approved by CEN on 10 June 2011.

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 CEN-CENELEC 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 CEN-CENELEC Management Centre has the same status as the official versions.

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Foreword

The text of ISO 13408-4:2005 has been prepared by Technical Committee ISO/TC 198 “Sterilization of health care products” of the International Organization for Standardization (ISO) and has been taken over as EN ISO 13408-4:2011 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 December 2011, and conflicting national standards shall be withdrawn at the latest by December 2011.

Attention is drawn to the possibility that some of the elements of this document may be the subject of patent rights. CEN [and/or CENELEC] shall not be held responsible for identifying any or all such patent rights.

This document supersedes EN 13824:2004.

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 Directives.

For relationship with EU Directives, see informative Annexes ZA, ZB, or ZC, which are integral parts of this document.

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, Croatia, 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 the United Kingdom.

Endorsement notice

The text of ISO 13408-4:2005 has been approved by CEN as a EN ISO 13408-4:2011 without any modification.

Introduction

During the process of preparing ISO 13408-1 several items, e.g. filtration, lyophilization drying and sterilization-in-place technologies, were found to be in need of supplementary information that was too voluminous to be given in corresponding annexes.

This part of ISO 13408 includes requirements and guidance that are to be observed during clean-in-place processes. The purpose of this part of ISO 13408 is to achieve standardization in the field of validation and routine control of clean-in-place processes used in the manufacture of health care products.

Clean-in-place processes allow parts of the equipment or an entire process system to be cleaned without being dismantled, reducing the need for disassembling and connections under clean conditions. For example, tanks, vessels, freeze-dryers piping and other processing equipment used for manufacture may be cleaned in place.

The clean-in-place process is in most instances followed by sterilization-in-place process (described in ISO 13408-5). While clean-in-place and sterilization-in-place methods differ considerably in technology, the concept of *in situ* treatment is similar.

Design considerations of all systems are critical to ensure that clean-in-place technologies can be successfully applied to clean manufacturing equipment to the desired level of cleanliness.

Aseptic processing of health care products —

Part 4:
Clean-in-place technologies

1 Scope

This part of ISO 13408 specifies the general requirements for clean-in-place (CIP) processes applied to product contact surfaces of equipment used in the manufacture of sterile health care products by aseptic processing and offers guidance on qualification, validation, operation and control.

This part of ISO 13408 is applicable to processes where cleaning agents are delivered to the internal surfaces of equipment designed to be compatible with CIP, which may come in contact with the product.

This part of ISO 13408 is not applicable to processes where equipment is dismantled and cleaned in a washer.

This part of ISO 13408 does not supersede or replace national regulatory requirements, such as Good Manufacturing Practices (GMPs) and/or compendial requirements that pertain to particular national or regional jurisdictions.

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 13408-1, *Aseptic processing of health care products — Part 1: General requirements*

ISO/IEC 90003, *Software engineering — Guidelines for the application of ISO 9001:2000 to computer software*

3 Terms and definitions

For the purposes of this document, the terms and definitions given in ISO 13408-1 and the following apply.

3.1
cleaning agent
organic or inorganic chemical including water, detergent or mixture thereof, used as an aid in the cleaning process for cleaning equipment

3.2
clean-in-place
CIP
method of cleaning of the internal surfaces of parts of the equipment or an entire process system without or with minimal disassembly

NOTE CIP also includes the removal of remaining residual cleaning agent to an acceptable level which is defined based on the nature of the product and the process tolerance.

3.3
dead leg
location which, by design, does not permit adequate accessibility of the cleaning agent

3.4
design qualification
documented verification that the proposed design of the facilities, equipment, or system is suitable for the intended use

3.5
material safety data sheet
document specifying the properties of a material, its potential hazardous effects for humans and the environment, and the precautions necessary to handle and dispose of the material safely

3.6
worst-to-clean
most difficult conditions for cleaning

EXAMPLES Materials to be removed, surface types to be cleaned, process parameters to be met or position(s) to be reached.

4 Quality system elements

4.1 General

4.1.1 The requirements of ISO 13408-1 shall apply.

4.1.2 Documented procedures for each phase of the development, validation, routine monitoring and control of the CIP process shall be prepared and implemented.

4.1.3 Documents required by this part of ISO 13408 shall be reviewed and approved by designated personnel.

4.1.4 Records of development, validation, routine control and monitoring shall be maintained to provide evidence of conformity to the requirements of this part of ISO 13408.

4.2 Management responsibility

4.2.1 The responsibilities and authority for implementing and performing the procedures described in this part of ISO 13408 shall be specified.

4.2.2 If the requirements of this part of ISO 13408 are undertaken by organizations with separate quality management systems, the responsibilities and authority of each party shall be specified.

4.3 Design control

Characterization of the cleaning agent(s), cleaning method, equipment to deliver CIP and the equipment subject to CIP, shall be undertaken in accordance with a documented plan. At defined stages, design reviews shall be planned, conducted and documented.

4.4 Measuring instruments and measuring systems

4.4.1 A documented system shall be specified for the calibration of all measuring instruments or measuring systems.

4.4.2 The accuracy and tolerance of the measuring instrument shall be justified for the process to be measured.

5 Process and equipment characterization

5.1 General concepts

5.1.1 The specification for the CIP process shall include but not be limited to:

a) physical and chemical properties of the material to be removed and the strength of its adherence to the surface from which it is to be removed;

b) physical and chemical properties and mechanism of action of cleaning agent(s);

c) compatibility of the equipment with the cleaning agents and processing conditions;

d) pre-cleaning period and conditions prior to cleaning;

e) the number of passes (single-pass cleaning, and/or multi-pass cleaning);

f) filling and immersing period with cleaning agent(s);

g) agitation or spraying of cleaning agent(s);

h) cleaning agent(s) elimination;

i) post-cleaning drying;

j) post-cleaning protection of the cleanliness of the equipment;

k) maximum post-cleaning hold period and conditions.

5.1.2 Cleaning agent(s) shall be reproducibly delivered in effective quantities and concentrations to all parts of the system.

5.1.3 In order to ensure effective CIP, all parameters necessary to control the cleaning conditions shall be established and documented. These conditions shall be maintained and monitored within specified limits.

5.1.4 When a large system is to be subjected to CIP, by dividing it into several segments, the segments should overlap to ensure that all portions of the system are adequately and effectively cleaned.

NOTE Although the entire processing system can be cleaned as a single entity in CIP, it can be advantageous to divide the system into several parts in order to simplify the cleaning procedures.

5.1.5 Complex sequences of opening and shutting of valves in the pipes of a system could be required. Where this is controlled manually, detailed documentation of individual steps shall be established. Where automation is used, electronic automation systems should be carefully designed and validated.

5.2 Effectiveness of CIP

5.2.1 The necessary level of cleanliness shall be established and documented. Justification of the process parameters and the permitted levels of residual substances shall be included in the documentation. There shall be no residue that poses a significant risk to patient safety.

NOTE Residual substances can include previous product or decomposition products thereof and/or cleaning agents.

5.2.2 Criteria for cleanliness are dependent in part, on the nature of the product that was previously processed in the equipment to be cleaned taking into account potency, toxicity, biocompatibility, carcinogenicity, mutagenicity, potential for tissue sensitization where equipment is not dedicated, etc. Where removal of product is not possible with sufficient efficacy, it may be necessary to use dedicated equipment.