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Aseptisk behandling av medicintekniska produkter – Del 3: Frystorkning (ISO 13408-3:2006)

Aseptic processing of health care products – Part 3: Lyophilization (ISO 13408-3:2006)

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Europastandarden EN ISO 13408-3:2011 gäller som svensk standard. Detta dokument innehåller den officiella engelska versionen av EN ISO 13408-3:2011.

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

The European Standard EN ISO 13408-3:2011 has the status of a Swedish Standard. This document contains the official version of EN ISO 13408-3:2011.

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

Förhållandet till övriga delar under samma huvudtitel - Utdrag ur Förord i ISO 13408-3:2011/ Relations to other parts under the same general title - Extract from the Foreword of ISO 13408-3:2011

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 13408-3

June 2011

ICS 11.080.01

Supersedes EN 13824:2004

English Version

Aseptic processing of health care products - Part 3: Lyophilization (ISO 13408-3:2006)

Traitement aseptique des produits de santé - Partie 3: Lyophilisation (ISO 13408-3:2006)

Aseptische Herstellung von Produkten für die Gesundheitsfürsorge - Teil 3: Gefriertrocknung (ISO 13408-3:2006)

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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EUROPÄISCHES KOMITEE FÜR NORMUNG

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Foreword

The text of ISO 13408-3:2006 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 13408-3:2011 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 13408-3:2006 has been approved by CEN as a EN ISO 13408-3:2011 without any modification.

Introduction

This part of ISO 13408 deals with lyophilization, which is a physical-chemical drying process designed to remove solvents from both aqueous and non-aqueous systems, primarily to achieve product or material stability. Lyophilization is synonymous to the term freeze-drying. Lyophilization involves freezing an aqueous system and removing the solvent, first by sublimation (primary drying) and then by desorption (secondary drying), to a level that no longer supports chemical reactions or biological growth. The result is a stable, well-formed product meant to rapidly disperse or solubilize while retaining biological or other activity. Because it is often the final step in an aseptic process with direct impact on the safety, quality, identity, potency and purity of a product, lyophilization is a critical processing step.

Where the finished lyophilized product is intended to be sterile, the product to be dried is an aqueous system that has already been sterilized. Therefore, all activities that can affect the sterility of the product or material need to be regarded as extensions of the aseptic processing of that sterilized product or material. In general, the predominant challenge in ensuring product or material sterility during lyophilization is to prevent microbiological and particulate contamination between the filling operation and completion of the lyophilization process. Of special, equipment-related concern is the protection of the product or material from microbiological contamination within the chamber.

Aseptic processing of health care products —

Part 3:
Lyophilization

1 Scope

This part of ISO 13408 specifies requirements for, and offers guidance on, equipment, processes, programmes and procedures for the control and validation of lyophilization as an aseptic process. It does not address the physical/chemical objectives of a lyophilization process.

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 9001, *Quality management systems — Requirements*

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

ISO 13408-4, *Aseptic processing of health care products — Part 4: Clean-in-place technologies*

ISO 13408-5, *Aseptic processing of health care products — Part 5: Sterilization in place*

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
lyophilization
physical-chemical drying process designed to remove solvents from both aqueous and non-aqueous systems, by sublimation and desorption

3.2
leak test
physical test for the capability to provide a quantifiable leakage rate under repeatable test conditions

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, control and maintenance of the lyophilizer 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 responsibility 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

The design of the lyophilizer shall be undertaken in accordance with a documented plan. At defined stages, design reviews shall be planned, conducted and documented. Software used to control and/or to monitor shall be prepared in accordance with a quality system that provides documented evidence that the software meets its design specification.

4.4 Measuring instruments and/or measuring systems

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

4.4.2 Procedures shall be specified for control of all measuring instruments and/or measuring systems designated as non-conforming, and for corrective action.

5 Product definition

5.1 The product to be lyophilized shall be defined and documented. The specification of the product shall include but not be limited to:

a) its chemical, physical and pharmaceutical properties as appropriate;

b) container and closure configuration.

5.2 Following application of the specified lyophilization process it shall be demonstrated that the product meets its specified requirements for safety, quality and performance.

6 Process definitions

6.1 A specification for the lyophilization process shall be documented.

6.2 The lyophilization process applicable for a defined product shall be established. Process development shall be performed to determine critical process parameters.

6.3 The process parameters, together with their tolerances, shall be established and documented. These shall include, but not be limited to:

a) the range of temperatures and pressures;

b) the rates of freezing;

c) the time at a given temperature and pressure.

6.4 During all processes the conditions achieved shall be monitored, maintained within specified tolerances, and recorded.

6.5 Where conditioning of the product is required prior to the lyophilization process it shall be defined and documented as part of the lyophilization process.

6.6 The following stages of the lyophilization process shall be evaluated to determine the relevance of maximum hold or wait times:

a) between the start of filling and the start of the lyophilization cycle;

b) between the end of the lyophilization cycle and the start of unloading (where stoppers are not seated into the product containers within the equipment prior to the opening of the lyophilizer chamber);

c) between sterilization of the lyophilizer and the start of the lyophilization cycle;

d) between sterilization and use of utensils (such as trays, bags, placing devices, tweezers etc).

6.7 Specifications for the Cleaning-in-Place (CIP) and Sterilization in Place (SIP) processes shall be documented. ISO 13408-4 and ISO 13408-5 shall apply.

7 User requirements

7.1 General

7.1.1 Documentation shall define clearly and precisely the equipment functionality and performance required but without regard as to how that functionality shall be designed or implemented. It shall be reviewed and approved by the user.

7.1.2 The product/process application shall be developed before designing the lyophilizer. The process conditions/parameters, together with their tolerances, shall be defined so that the use of the lyophilizer and the ancillary equipment will produce a reliable and safe product.

7.2 Equipment characterization

7.2.1 Design specifications for equipment to deliver the required processes within defined tolerances shall be established and documented.

7.2.2 The equipment shall be designed, built and located so as to facilitate aseptic processing, cleaning, sterilization and lyophilization. For CIP and SIP, ISO 13408-4 and ISO 13408-5 shall apply.

7.2.3 The design shall address such issues as the internal surfaces and the surrounding environment from the prior processing step through to loading and unloading, with special attention to the position of equipment, personnel and critical processing zones.

7.2.4 The design of the lyophilizer shall permit effective cleaning and sterilization of chamber and condenser.

7.2.5 Blocks, cassettes, frames, shelves, trays etc. required for the lyophilization process shall be defined and documented as part of the process.

NOTE Flat shelves are desirable for even product contact for both reasons of temperature uniformity and the distribution of mechanical pressure (e.g. during stoppering in the case of vials with stoppers) and for the prevention of condensate retention.

7.2.6 The maximum permitted leakage of air into the lyophilizer shall be specified.