INTERNATIONAL STANDARD

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# Aseptic processing of health care products —

## Part 3: Lyophilization

*Traitement aseptique des produits de santé —*
*Partie 3: Lyophilisation*



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# Foreword

ISO (the International Organization for Standardization) is a worldwide federation of national standards bodies (ISO member bodies). The work of preparing International Standards is normally carried out through ISO technical committees. Each member body interested in a subject for which a technical committee has been established has the right to be represented on that committee. International organizations, governmental and non-governmental, in liaison with ISO, also take part in the work. ISO collaborates closely with the International Electrotechnical Commission (IEC) on all matters of electrotechnical standardization.

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 13408-3 was prepared by Technical Committee ISO/TC 198, *Sterilization of health care products*.

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*

## 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.