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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.

7.2.7 If compressed air, nitrogen or any other gas is admitted into the lyophilizer, its purity and rate of admission shall not impair the integrity of the product.

7.2.8 Equipment controls in the critical processing zone shall be minimized.

7.2.9 The specification for the location in which the equipment and its components are to be installed shall be established and documented and include (but not be limited to):

a) the services that are required for the lyophilizer and for the area in which it is installed;

b) the materials of construction for the parts that transport the utilities to and from the lyophilizer.

7.3 Product handling

7.3.1 Transport to, and loading of, the lyophilizer

7.3.1.1 A procedure for loading the lyophilizer, including the loading pattern within the chamber, shall be specified and documented.

7.3.1.2 Transport to the lyophilizer and loading of the filled product, utensils or other equipment into the lyophilizer shall take place in a critical processing zone. Where auxiliary equipment or containers are used for transport, the validated conditions maintained therein shall be equivalent to the critical processing zone.

7.3.1.3 Airflow patterns resulting from transport devices and venting of the loading zone where the unsealed containers are exposed shall maintain critical processing zone conditions.

7.3.1.4 Utensils used during transfer to, and loading of, the lyophilizer that could contaminate the product shall be subjected to a validated sterilization process.

7.3.2 Unloading the lyophilizer

7.3.2.1 A procedure for unloading the lyophilizer shall be specified and documented.

NOTE Seating of the stoppers is normally performed within the lyophilizer chamber prior to unloading.

7.3.2.2 Where seating of the stoppers is not completed prior to opening the lyophilizer chamber, product removed from the lyophilizer shall remain in a critical processing zone during subsequent handling.

7.3.2.3 Utensils used during unloading of lyophilizer and transfer shall be subjected to a validated disinfection and/or sterilization process.

7.4 Microbiological and particulate environmental monitoring

A programme for microbiological and particulate monitoring of the environment during product transfer and lyophilization shall be defined and documented.

7.5 Cleaning and sterilization

7.5.1 Cleaning-in-place (CIP)

For CIP processes ISO 13408-4 shall apply.

7.5.2 Manual cleaning

7.5.2.1 The cleaning process shall be specified and shall be capable of being validated to provide an adequate challenge that represents the worst-case conditions experienced during routine operation and cleaning of the equipment.

7.5.2.2 The process shall be sufficient to prevent chemical and particulate contamination of the product or material during the lyophilization process, and to remove any residues that would otherwise create a barrier between the sterilizing agent and the equipment surfaces.

NOTE An automated process is preferred in order to improve consistency, reliability and personal safety.

7.5.3 Sterilization in place (SIP)

7.5.3.1 For sterilization in place processes, ISO 13408-5 shall apply.

7.5.3.2 The lyophilizer shall be sterilized before each load or, under defined circumstances, before each campaign.

A limit to the number of dryer loads in a campaign should be specified and validated.

7.5.3.3 Conditions protecting the lyophilizer from contamination after sterilization shall be maintained, the efficacy of the protection shall be validated and the performance documented.

7.5.3.4 In the case of a closing system for pre-plugged vials, sterilization of the ram protruding into the chamber should be addressed where applicable.

7.6 Vent filter system

7.6.1 Bacteria retentive filters shall be used to maintain lyophilizer integrity when breaking the vacuum. Flow or pressure increase rate shall be specified, documented and justified.

7.6.2 The filter assembly shall be sterilized in conjunction with chamber and condenser, without damaging the filter.

NOTE *In situ* filter sterilization is preferred.

7.6.3 The frequency of the filter integrity testing shall be specified, justified and documented.

7.7 Lyophilizer leak test

7.7.1 The lyophilizer shall comply with user-defined leak test procedures and limits.

7.7.2 Procedures shall be documented and shall include such aspects as the frequency of routine testing, the targeted vacuum conditions (depth and duration), the maximum permitted leakage of air into the lyophilizer chamber and condenser, as well as the alert limits and rationale behind possible corrective actions.

8 Validation

8.1 General

Written protocol(s) shall be established and shall specify how validation is to be conducted. Protocol(s) shall be reviewed and approved and shall specify critical parameters and acceptance criteria. Validation of equipment design, installation, operation, performance and processes shall be performed by qualified personnel in accordance with the approved protocol(s). Any deviation from the protocol(s) shall be documented, investigated and resolved.

8.2 Design qualification

Appropriateness of system design and design of the facilities, utilities, equipment and materials used shall be confirmed to meet the requirements for the intended use at the first stage of validation.

Design qualification should be emphasised in validation activities as specified in ISO 9001.

NOTE Design qualification is documented verification that the proposed design of the facilities, utilities, equipment and system is suitable for the intended use.

8.3 Installation qualification

8.3.1 General

Installation qualification shall be carried out in accordance with a documented procedure that cross-references appropriate equipment and "as installed" specifications.

8.3.2 Installation

8.3.2.1 It shall be documented and verified that the equipment and its location conform to its specification.

8.3.2.2 It shall be documented and verified that the equipment is installed in accordance with the installation instructions.

8.3.2.3 It shall be documented and verified that the services to the equipment conform to their specification.

8.3.2.4 The calibration of all measuring chains (including any test instruments) used for monitoring, controlling, indicating or recording shall be verified.

8.3.2.5 The operating instructions shall be available and shall reflect the manner in which the equipment is to be operated during operational qualification.

8.3.2.6 Requirements given in 8.3.2.4 and 8.3.2.5 may be confirmed at the commencement of operational qualification.

8.3.3 Computer and software qualification

Computerized control systems and associated software shall be qualified before starting operational tests on the equipment to demonstrate conformance to the specification.

8.3.4 Alarm systems

The alarm system shall be qualified to demonstrate conformance with specifications and to demonstrate that the appropriate control system responses are observed and documented.

8.4 Operational qualification

8.4.1 General

Operational qualification shall be performed in accordance with documented procedures to demonstrate that the installed equipment is capable of delivering the specified processes within defined tolerances.

8.4.2 Leak test

A leak test shall be performed to demonstrate conformance with the specification. The leakage of air into the lyophilizer chamber shall not exceed the specified limits.

8.4.3 Thermal control system(s)

The system(s) that control temperatures shall be qualified to demonstrate that the rate of thermal control and ultimate temperature capabilities of the system conform to the specification(s).

NOTE Thermal control system(s) are used to control variables such as shelf temperature, condenser temperature, and jacket temperature.

8.4.4 Vacuum system

The vacuum system shall be qualified to demonstrate that the rate of evacuation and the ultimate capabilities of the vacuum system conform to the specification.

8.4.5 Condenser refrigeration

The refrigeration system capacity and cooling rate of change shall be qualified to demonstrate conformance with the specification.

Operational qualification is the first check of the condenser capacity and may be done with a reference solvent such as water.

8.4.6 Defrosting

Where a defrost cycle is specified, the sequence of operations shall be performed to demonstrate conformance with the specification.

8.4.7 Lyophilization cycle

The sequence of operation of the lyophilization cycle shall be performed to demonstrate conformance with the specification.

8.4.8 CIP cycle

Operational qualification shall be performed in accordance with documented procedures to demonstrate compliance with the requirements of ISO 13408-4.

8.4.9 SIP cycle

Operational qualification shall be performed in accordance with documented procedures to demonstrate compliance with the requirements of ISO 13408-5.

8.4.10 Stoppering seating system(s)

Stoppering seating system(s), where present, shall be qualified to demonstrate conformance to their specification.

8.4.11 Shelf temperature distribution

8.4.11.1 Shelf temperature distribution studies shall be performed to identify inter- and intra-shelf variations and shall demonstrate conformance to the specification.

Ideally, these studies should be performed with the chamber at atmospheric pressure and include a range of temperatures that take into account both the heating and cooling phases of the lyophilization cycle.

8.4.11.2 The number of temperature sensors used shall be specified.

8.5 Performance qualification

8.5.1 General

Data generated during installation qualification and operational qualification shall be reviewed before performance qualification is started to verify that the requirements of both performance qualification and process validation will be met.

Usually, performance qualification is performed with actual product. However, where a well-characterized equivalent placebo is available, this may be used.

8.5.2 Lyophilization

8.5.2.1 Performance qualification shall be performed to demonstrate the suitability of the equipment for the intended product or process.

8.5.2.2 The lyophilizer shall be loaded with product or placebo, in accordance with documented procedures, and processed to demonstrate conformance to the predetermined cycle parameters.

8.5.3 SIP

Performance qualification shall be performed, in accordance with documented procedures, to demonstrate compliance with the requirements of ISO 13408-5.

8.6 Process validation

8.6.1 General

Process validation shall be performed to demonstrate that the lyophilization process leads to the intended product quality and characteristics.

NOTE Subparts of process validation are process simulation, cleaning and product qualification simulating routine production.

8.6.2 Cleaning validation

Cleaning of the lyophilizer shall be validated. CIP processes shall be validated in accordance with the requirements of ISO 13408-4.

8.6.3 Process simulations

NOTE 1 Process simulations representing the aseptic processing of lyophilized products include extra difficulties associated with manipulative activities and human intervention.

NOTE 2 Concerns related to the introduction of microbiological media into a lyophilizer are minimized by a combination of working, cleaning, disinfection and sterilization methods, which make the use of liquid broth solutions in lyophilizers acceptable.

8.6.3.1 The process simulation procedure for lyophilized products shall represent the entire aseptic processing chain, including filling, transport, loading, chamber dwell, unloading and sealing, under specified, documented and justified conditions representing worst case operating parameters.

8.6.3.2 The lyophilizer process simulation shall duplicate as much of the lyophilization process, except freezing, as practical, including partial vacuum and duration as appropriate for the media. Boiling-over or actual freezing of the solution shall be avoided.

Factors to consider include, where applicable:

a) use of air instead of nitrogen;

b) maximum interval between sterilizations of the lyophilizer;

c) maximum period of time between sterilization and lyophilization;

d) quantitative aspects of worst-case situations.

NOTE An example is the number of trays loaded and duration of loading (chamber open to environment).

8.6.4 Product validation

8.6.4.1 The lyophilized product shall be tested to ensure that predetermined quality attributes conform to specifications and that product requirements for safety, quality, identity and purity are met.

Quality attributes to be tested for should include (but not be limited to) sterility, stability, residual solvent, reconstitution, appearance, potency and uniformity.

8.6.4.2 Testing shall be performed in accordance with an approved sampling plan.

8.7 Review and approval of validation

Information gathered or produced during design qualification, installation qualification, operational qualification, performance qualification and process validation shall be reviewed for conformity to the acceptance criteria specified for each element of the validation process. The results of this review shall be documented.

9 Routine monitoring and control

9.1 General

The purpose of routine monitoring and control is to demonstrate that the validated and specified processes have been delivered.

9.2 Operator training

9.2.1 Operators shall be trained according to established procedures.

9.2.2 Specific operator training shall be implemented in accordance with a documented programme. Training shall demonstrate the operator's:

a) understanding of the principles of the process, including operational and construction features;

b) ability to perform the routine operation;

c) understanding of the actions to be taken if a process or any part of the process fails;

d) understanding of the safety aspects of the systems.

9.3 Standard operating procedures

Established and documented operational procedures based on the validated parameters shall include, but not be limited to:

a) step-by-step operating instructions;

b) acceptance criteria for the operating cycle parameters, and actions to be taken if those criteria have not been met;

c) duties and responsibilities;

d) housekeeping, calibration and maintenance instructions.

9.4 Requalification

9.4.1 Requalification of the aseptic process shall be performed at defined intervals in accordance with a documented plan.

9.4.2 Records shall be retained of the reviews of requalification data and of any corrective actions taken when the specified acceptance criteria are not met.

9.5 Maintenance of equipment

Preventative maintenance shall be planned and performed in accordance with documented procedures.

9.6 Change control

9.6.1 A change to equipment, product, packaging, presentation or orientation in the lyophilizer shall be assessed for its impact on the effectiveness of the processes.

The magnitude of the change should be considered in determining the extent to which installation qualification, operational qualification, performance qualification and process validation are undertaken.

9.6.2 The outcome of the assessment, including the rationale for any decisions reached and the extent of qualification that is necessary, shall be documented.

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