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Aseptic processing of health care products —

Part 4: Clean-in-place technologies

Traitement aseptique des produits de santé —

Partie 4: Technologies de nettoyage sur place

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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 13408-4 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*

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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.

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Aseptic processing of health care products —

Part 4:
Clean-in-place technologies

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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.

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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.

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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.

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5.3 Equipment

5.3.1 Equipment to be subjected to CIP

5.3.1.1 The equipment shall be designed and manufactured to ensure its cleanability by taking into account ease of cleaning with regard to the characteristics of the products to be processed. Worst-to-clean locations shall be minimized through the use of smooth, impervious, non-grooved, continuous and polished surfaces.

NOTE Dead legs, locations with stagnant liquid in piping, shoulders of tanks, intricate irregular internal surfaces such as gasket interfaces and pump internal parts can usually be regarded as worst-to-clean locations.

5.3.1.2 Design considerations shall include but not be limited to:

a) smoothness of inner surface of equipment;

b) distribution of the cleaning agent(s) to all relevant surfaces (e.g. valves, connections, filter assemblies);

c) necessity to use special equipment such as spray devices, their number, location and coverage;

d) absence of dead legs in piping systems;

e) drainability of the system (e.g. slope of piping to ensure the complete removal of remaining liquid in the system);

f) compatibility of materials of construction (e.g. pipes, tanks, valves, nozzles, filters, gaskets, sensors) with the cleaning agent(s) and process conditions selected;

g) access to allow monitoring of cleaning conditions in appropriate locations;

h) protection of the cleaned equipment from re-contamination.

5.3.1.3 Specification of the equipment shall include but not be limited to:

a) physical description of the equipment, together with any necessary ancillary items, including materials of construction, (including as-built drawings);

b) specifications of the cleaning agent and means by which it is provided, including any additives or precursors necessary for its delivery;

c) description of instrumentation for monitoring and controlling the cleaning process, including sensor characteristics and their locations, indicating and recording instruments;

d) description of safety features, including those for personnel and environmental protection;

e) description of installation requirements, if applicable;

f) documented evidence that the software used to control and/or monitor the process is prepared in accordance with a quality system and that the software meets its design intention;

g) a process flow diagram which outlines the processing equipment layout to be cleaned, including valve sequencing.

5.3.2 Equipment to be used for CIP

5.3.2.1 The equipment shall be designed and manufactured to effectively perform and control CIP of the equipment to be cleaned. Primary functions to be verified in qualification shall include but not be limited to:

a) preparation and storage of cleaning agent(s);

b) admittance of cleaning agent(s) into the equipment to be cleaned in a controlled and safe manner;

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c) distribution of cleaning agent(s) within the equipment to be cleaned;

d) maintenance of effective cleaning conditions throughout the equipment to be cleaned, (e.g. delivery pressure and delivery temperature).

5.3.2.2 Specification of the equipment shall include but not be limited to:

a) physical description of the equipment, together with any necessary ancillary items, including materials of construction, (including as-built drawings);

b) specifications of the cleaning agent and means by which it is provided, including any additives or precursors necessary for its delivery;

c) description of instrumentation for monitoring, controlling and recording the cleaning process, including sensor characteristics, and their locations, indicating and recording instruments;

d) description of safety features, including those for personnel and environmental protection;

e) description of installation requirements, if applicable;

NOTE This can include, for example, the location and the environment in which the equipment is to be installed and the services that are required for the CIP and for the area in which the CIP system is installed.

f) documented evidence that the software used to control and/or monitor the process is prepared in accordance with a quality system and that the software meets its design intention.

5.3.3 Failure detection

Means shall be provided to ensure that a failure in a control function does not lead to any failure in recording of process parameters such that an ineffective process appears effective.

6 Cleaning agent characterization

6.1 Selection of cleaning agent(s)

6.1.1 Only cleaning agent(s) that have been shown to be suitable for their intended purpose shall be used. For selection of the most suitable cleaning agent(s) at least the following considerations shall be addressed:

a) physical and chemical characteristics of residual substances to be removed;

b) characteristics of potential cleaning agent(s);

c) compatibility with the manufacturing equipment;

d) ability to remove residual cleaning agent(s) including a method to detect residual cleaning agent(s).

6.1.2 It may be necessary to remove any remaining residuals of cleaning agent(s) by using secondary cleaning agent(s), such as purified water or water for injection as appropriate.

NOTE Examples of cleaning agent(s) include water, hot water, detergents, alkaline solution, hot alkaline solution, organic solvents, or acids.

6.2 Quality of cleaning agent(s)

Quality specifications for the cleaning agents shall be established, justified and documented. In establishing a specification, at least the following shall be considered:

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a) identity of the cleaning agent(s);

b) chemical composition and bioburden;

c) assurance of strength or concentration;

d) shelf life.

6.3 Safety and the environment

6.3.1 A material safety data sheet or analogous safety information for the cleaning agent(s) shall be available.

6.3.2 An assessment of the potential environmental impact of the cleaning agent(s) shall be available.

7 CIP process

7.1 Process parameters

7.1.1 The cleaning method shall be determined by considering the construction features of the equipment to be cleaned, and by considering the physical and chemical characteristics of residual substances.

7.1.2 Process parameters as justified in 5.2, including minimum and maximum limits, shall be defined and documented. Process parameters shall be adequate to ensure cleaning of equipment to the previously determined acceptable level.

Such parameters shall include, as appropriate:

a) flow rate and pressure;

b) type and concentration of the cleaning agent(s);

c) temperature of cleaning agent(s);

d) time for priming the system, undertaking the CIP process, inactivation/rinsing and draining/drying the product contact surfaces;

e) total time of cleaning including rinsing and drying as appropriate;

f) agitator motion;

g) volume of cleaning agent and rinse water.

7.1.3 A worst-case assessment shall be performed and documented when multiple products are manufactured using the same equipment. This assessment is intended to identify the most difficult to remove residual product as well as the most toxic residues to be removed.

NOTE Indicator products are frequently used as worst case and the CIP validation can be based on these as an alternative to validating each single substance or product.

7.2 Process control

7.2.1 General

Means of monitoring and controlling the process parameters shall be defined and documented.

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7.2.2 Selection of sampling method(s)

The sampling method(s) shall be established with a rationale by considering the construction features of the equipment, and also by considering the physical and chemical characteristics of the product. Sampling methods are described in Annex A.

NOTE 1 Usually, a combination of visual inspection, swab method and rinse methods is used.

NOTE 2 Examples for analytical methods to determine the amount of residual substances are HPLC, TLC, TOC, UV absorption method, pH, ion-strength, conductivity, osmotic pressure, colour, smell and/or visual inspection.

7.2.3 Analytical methods and sample method validation

The specificity and sensitivity of analytical methods and the recovery using the sampling method shall be determined and validated. The method shall be valid in the presence of other materials (e.g. cleaning agents). Recovery efficiency results for any sampling method shall be factored into the test results.

7.2.4 Acceptance criteria

Acceptance criteria shall be based upon a calculation of theoretical carryover into the next batch. A documented rationale shall be written which specifies the acceptance criteria for cleaning. When calculating carryover into next batch, potential distribution of residue in total rinse or first pass should be considered.

NOTE Acceptance criteria can also be based on toxicity, analytical detectability and process capability of the CIP process.

7.2.5 Visual examination

Visual examination shall be performed using approved procedures and trained operators looking for visible contamination. Procedures shall include requirements for lighting or visual aids.

7.2.6 Chemical examination

A method to determine chemical residuals shall be established. The effectiveness of the CIP procedure shall be determined.

Chemical residuals shall be established, either:

a) directly, by quantifying the amount of residual present on the surface of the equipment or in the rinse, or

b) indirectly by measuring parameters correlated with the residual, e.g. conductivity or TOC.

Acceptance criteria shall be evaluated against the products and specified in the validation protocol with proper justification. Examples for calculation are given in Annex B.

7.2.7 Microbiological examination

7.2.7.1 The ability of CIP processes to remove microbial contamination may be included in CIP validation, using surface swabbing or rinse samples.

7.2.7.2 Acceptance criteria shall be based upon efficacy of any subsequent processing (sterilization).

7.2.7.3 Validation should provide evidence that routine CIP and storage of equipment does not allow microbial proliferation.

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7.2.8 Endotoxin

7.2.8.1 For products with an endotoxin specification, the level of endotoxin on the equipment shall be evaluated as part of CIP validation.

7.2.8.2 For products with an endotoxin specification, the level of endotoxin on the equipment shall meet compendial requirements.

7.2.9 Particulates

CIP shall remove all particles and foreign matter to specified levels consistent with the requirements of the product intended to be manufactured in the equipment.

NOTE Visual inspection is the primary methodology for verifying the absence of bristles, fibres, etc. For smaller (sub-visible) contamination, rinse samples can be taken to validate the capability of the process to achieve acceptable and reproducible results.

7.3 Residues of cleaning agent(s)

After the CIP process has been completed, any cleaning agent(s) shall be removed from the system. Permissible levels of residues shall be specified and justified.

8 Validation

8.1 Validation protocol

Written protocol(s) shall be established, and specify how qualification and validation are to be conducted. Protocol(s) shall be reviewed and approved and specify critical steps and acceptance criteria. Qualification of equipment design, installation, operation and performance shall be performed in accordance with the approved protocol(s). Any deviation(s) from the protocol(s) shall be documented, investigated and resolved.

8.2 Evaluation of the CIP process

Acceptance criteria for the validation of CIP shall be established based on the evaluation of cleanliness and ability to remove cleaning agent residue (see Clause 7).

8.3 Design qualification

The CIP system shall be designed for its intended use. Appropriateness of system design, process design, design of all facilities, equipment and materials used shall be confirmed at the first stage of validation to meet the requirement for the intended use.

8.4 Installation qualification

8.4.1 General

Installation qualification shall be performed to demonstrate that the equipment used to perform CIP and deliver the cleaning agent, and the equipment to be subjected to CIP, and any ancillary items have been supplied and installed in accordance with their specifications.

8.4.2 Installation

8.4.2.1 It shall be verified that

a) the location of the equipment conforms to its specification,

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b) the equipment is installed in accordance with installation instructions,

c) the services to the equipment conform to their specification(s).

8.4.2.2 The calibration of all measuring instruments critical to the process (including any test instruments) used for monitoring, controlling, indicating or recording shall be confirmed.

NOTE Alternatively, calibration can be confirmed at the commencement of operational qualification.

8.4.2.3 Computerized control systems and associated software when installed, shall be qualified to demonstrate conformance to ISO/IEC 90003 or other relevant guidelines for the manufacture of the product.

8.5 Operational qualification

8.5.1 Operational qualification shall demonstrate that the installed equipment is capable of performing the specified CIP process throughout the equipment within defined parameters.

8.5.2 The operating procedures for the equipment shall be verified to meet established requirements. These operating procedures shall include but not be limited to:

a) step-by-step operating instructions;

b) the method by which a failure to attain the operating cycle parameters can be identified, and the actions to then be taken;

c) housekeeping, calibration and maintenance instructions;

d) the means by which an error in the result of a measurement for control, indication and recording can be identified;

e) details of contacts for technical support.

8.5.3 The consequences of failure in the result from each measuring instrument fitted to the CIP system (control, indication and recording) shall be determined at significant parts of the CIP system.

8.6 Performance qualification

8.6.1 Data generated during installation qualification and operational qualification shall be approved before performance qualification is started.

8.6.2 A successful CIP run shall be determined by operation within specified operating parameters, and achievement of defined acceptance criteria determined by visual, swab method and/or rinse methods. Data shall be collected to demonstrate that the CIP process achieves predetermined residual limits.

8.6.3 Performance qualification shall include a series of at least three consecutive and successful runs of the CIP process to demonstrate the reproducibility and effectiveness of the process.

If failure can be attributed to factors not relevant to the effectiveness of the CIP process being validated, this test can be documented as unrelated to performance of the CIP process without requiring three further consecutive, successful runs.

NOTE Examples of this type of failure include, but are not limited to, power failures, loss of services, or failure of external monitoring equipment.

8.6.4 Performance qualification studies shall be performed with the cycle parameters set to the least favourable limit (ensuring "worst-to-clean" conditions and locations yielding acceptable CIP effectiveness). The outcome of such studies shall predict that, on application of the CIP process, the specified requirements for cleanliness will be met.

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8.6.5 CIP process qualification shall be performed at the maximum period after use before the equipment is cleaned.

8.6.6 The number and locations of sampling for confirmation of cleanliness shall be specified. Documented evidence shall be provided to show that the number and locations used are sufficient to demonstrate that the requirements for cleanliness in the CIP system are met. Locations sampled shall address worst-to-clean locations.

8.7 Review and approval of validation

8.7.1 Information gathered or produced during design qualification, installation qualification, operational qualification and performance qualification shall be documented and reviewed for acceptability. The results of this review shall be documented.

8.7.2 A complete process specification, including the process parameters and their tolerances shall be confirmed. This process specification shall also include the criteria for designating an individual CIP process as conforming or acceptance criteria.

8.7.3 The validation report(s) shall be generated. The report(s) shall be signed by persons designated as responsible for preparing, reviewing and accepting this(these) report(s) against the acceptance criteria in the validation protocol(s).

8.7.4 The validation report(s) shall include a verification that all gauges, recorders etc., were within calibration at the time of the performance qualification.

8.8 Requalification

8.8.1 Requalification of processes carried out with specified equipment shall be performed at defined intervals and in response to CIP process failures.

8.8.2 CIP process data shall be reviewed periodically against specified acceptance criteria in accordance with documented procedures. Records of reviews of revalidation data, and corrective actions taken in the event that the specified acceptance criteria are not met, shall be retained.

8.8.3 Requalification report(s) shall be documented and retained.

9 Routine monitoring and control

9.1 CIP process control

Routine monitoring and control shall be performed on each CIP process. Data shall be recorded to demonstrate that the validated and specified CIP process parameters have been delivered to the system.

9.2 Procedures

Written procedures shall be consistent with those of validation studies. These procedures shall include but not be limited to:

a) step-by-step operating instructions;

b) duties and responsibilities;

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

d) housekeeping, calibration and maintenance instructions;

e) detailed description of the CIP process.

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9.3 CIP process records

9.3.1 CIP process records shall include but not be limited to:

a) date of operation;

b) name of process and lot (batch) number that is produced before CIP;

c) name of operator(s);

d) CIP process parameters and their confirmation.

Records can include equipment printout of contact time, temperature, pressure measured at predetermined positions, alarms or other parameters which influence cleaning efficacy, such as identification and concentrations of cleaning agents.

9.3.2 CIP process records shall be reviewed and accepted prior to the manufacturing of the next batch.

9.4 Change control

9.4.1 Changes to equipment, cleaning agent(s), process parameters or product processed on the equipment shall be assessed for their potential impact on the effectiveness of the CIP process and the need for requalification.

9.4.2 The magnitude of the change should be considered in determining the extent to which installation qualification, operational qualification or performance qualification is undertaken.

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

9.5 Maintenance and calibration

Preventive maintenance including calibration of instruments shall be planned, performed and documented in accordance with documented procedures.

10 Personnel training

10.1 Personnel shall be trained according to established procedures.

10.2 A specific training programme for personnel shall be established, implemented and documented. Training shall demonstrate the personnel's:

a) understanding of the theory and operation of CIP process, including construction features;

b) ability to perform the routine operation, maintenance or testing as appropriate;

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

d) understanding of the safety aspects of the cleaning agent(s) and CIP system.

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