Dec.8,2001

Doc.ISO/TC 198/WG 9
Drafted as a supplemental Normative Annex of "Aseptic Processing of Health Care Products-
Part 4-2, Sterilization-in-Place- (Steam)"
Based on the Resolution of ISO/TC 198/WG9 September 18-20, 2000 at Berlin

Normative Annex for Steam Sterilization –in –place

(Drafted by Dr. K.Kawamura)

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Purpose and scope

This normative annex for steam sterilisation-in-place is a supplement to ISO 13408 Part 4-2. It specifies the requirements for validation and routine monitoring of steam sterilisation-in-place processes.

Definition
(1). Design qualification

(2). Steam SIP (Steam Sterilization-in-Place)

Steam Sterilization-in-place (Steam SIP) enables a processing system to be sterilized as a single entity, thereby eliminating or reducing the need for aseptic connections. Tanks, Vessels, freeze-dryers, filling lines, transfer lines, filtration systems, water for injection and other processing equipment used for the manufacturing of sterile products may be sterilized in situ or in place without disassembling the components. This chapter specifies the essential parts of Steam SIP.

2. System Design of Steam SIP

.2.1. General Concept and Requirements for Steam SIP

Although the entire processing system can be sterilized as a single entity with

steam SIP, it may be advantageous to divide the system to several overlapping parts in order to simplify the sterilization procedures. When a large system is sterilized by dividing to several segments, the segments must overlap to ensure that all portions of the system are adequately sterilized. Steam is introduced to the system so that itcan spread throughout the system uniformly.

2.1.1. Steam should be introduced from higher portions in each portion of the system and condensate eliminated at all low points in the system.

2.1.2. In order to ensure effective sterilization, all parameters to control the sterilization conditions shall be maintained within specified conditions.
Process parameters of temperature, pressure and time, including their minimum and maximum limits, shall be determined by physical and microbiological performance qualification.

2.1.3. The conduct of a SIP process requires the precise execution of a number of intricate procedures for the control of sterilization conditions.
Note Some or total operations may be automated for these intricate procedures. When automation is utilized, electronic automation system should be carefully designed and validated.

2.1.4. Design of the system shall permit complete displacement and elimination of entrapped air, constant bleeding of steam at all low points to eliminate accumulation of condensate, and maintenance of sterility after completion of the sterilisation process.

2.2.Equipment used for Steam SIP

2.2.1. Inner surface of equipment
Inner surfaces of equipment, such as tanks and vessels, shall be smooth and designed to prevent air pocket or dead legs.

(1)In case of steam sterilization, inner corner or shoulder of the tank and/or vessel should be designed not to cause any air pocket, or the corner or shoulder does not entrap air or retain condensate.

(2)Materials of equipment used (pipes, tanks, valves, nozzles, filters, gaskets and others) shall be resistant to corrosion by frequent and repeated sterilization. Particularly, attention shall be paid to materials made of plastics and rubber , such as gaskets. The inlet of steam shall be located such as to allow the steam to spread homogeneously in the system.

(3) Bleed valves and condensate drains shall be installed at the end of each horizontal leg and at all low points in the system. Valves, drains, dead ends, low points and gas filters and housings within the system where air may become entrapped and/or where condensate may accumulate are the most difficult to sterilise locations in a SIP system. Procedures shall ensure that the SIP process is adequate to ensure sterilisation of equipment to the previously determined sterility assurance level.

2.2.2.Filter, Drainage, Bleeder, and Pressure Differential
Steam used for the SIP shall be introduced to the system through a microbially

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retentive filter"

(a) Condensate drainage shall be provided at the lowest part on both the sterile side and non-sterile side of each filter housing.

(c)Steam bleeds shall be provided , if necessary, on any part of the filter housing that might create an air pocket.

(d)Air pressure differential between the inlet and outlet sides of filters shall be balanced.

(e)Steam pressure and differential pressure shall be monitored and temperature shall be measured downstream of the filter.

(f)Cartridge filters shall be oriented so that condensate drainage from both sides of the filter surface is enhanced.

2.3. Piping used for steam sterilization

2.3.1.The innside of piping systems shall be smooth and designed so as not to cause any entrapped air. Piping system shall be designed to maintain a constant pressure and constant flow of the steam in the whole of the system.

2.3.2. Any dead ends of piping shall be of minimum length and unnecessary branches or dead ends shall be eliminated.

2.3.3.The inlet(s) of steam shall be located to optimize the replacement of the air inside the system with saturated steam

2.3.4.Steam bleeds and condensate drainage shall be installed in the lowest part of each part of the system to enable the continuous and smooth removal of the condensate.

2.3.5.Piping shall be sloped to the drainage to enable the complete removal of the condensate.

3.Quality of steam and Gas (Air or Nitrogen) used for SIP

(1). "Quality of the steam shall be defined. Verification of the specification should be provided by validation of the distribution system and a continuous regular monitoring."

Note: Air or non-condensable gas in steam, liquid water, oils from compressor and other contaminants should be controlled according to the specifications of steam.

(2). "Steam used for SIP shall be free from oil and shall not contain significant amount of particles. It shall be free from other aditives or impurities."

(3). "Steam used for the SIP shall be saturated steam without significant amount of other vapor or gases".

(4). Steam used for the SIP should not contain significant amounts of condensate droplets.

(5) Steam used for the SIP shall not be overheated nor superheated.

(Reference shall be made to other ISO documents concerning the moist heat sterilization on steam quality.)

4. Requirements for the materials of equipment and system to be sterilized in-place

(1).The effects of exposure to steam on the physical and/or chemical properties of materials, and on their biological safety shall be assessed.

NOTE: The materials should be selected on the basis of the frequent usage of the steam.

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(2). The effect of repeated exposure of equipment/system material/s to steam shall be investigated to ensure that functionality and safety are not compromised.

(3).The materials tested and the outcomes of all tests shall be documented, together with the criteria against which the properties of materials are assessed before and after exposure to steam.

5. Process and equipment characterization of Steam-SIP

NOTE: The purpose of this activity is to define the entire sterilization process and the equipment necessary to deliver the sterilization process safely and reproducibly.

5.1.Process of Steam SIP

(1) Process parameters together with their tolerance shall be established and □documented.□These tolerances shall be based upon a knowledge of the □□ □combination of process□parameters that cause the specified sterilising conditions □

□to be uniformly and reproducibly obtained in all parts of the equipment and □ □system.

(2) Means of monitoring and controlling the process variables shall be determined.

5.2. Equipment used for SIP

(1) The specification for equipment to sterilize the system shall be established to keep the system within the tolerances stipulated for the process parameters and in a safe manner and shall be documented.

(2) The specification shall include but is not limited to:

a) physical description of the equipment, together with any necessary ancillary items, including materials of construction;

b) specifications of steam and means by which it is provided.

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

d) fault recognized by the sterilizing equipment;

e) safety features, including those for personnel and environmental protection;

f) installation requirements, including for the control of emissions, if applicable.

(3) Where provided, Software used to control and/or monitor the process shall be prepared in accordance with a quality system that provides documented evidence that the software meets its design intention.

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

NOTE This may be achieved either by the use of independent systems for control and monitoring, or a crosscheck between control and monitoring which identifies any discrepancies and indicates a fault.

5.3. Requirement for Equipment and System to be Sterilized in Place:

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(1) The equipment and the system shall be designed and installed by considering the compatibility with steam used, and the product manufactured.
All equipment and systems to which Steam SIP is applied shall be designed and installed to allow the complete sterilization of the system. For this purpose, steam used shall be distributed homogeneously in the sterilized system. Equipment and components shall be resistant to frequent and repeated sterilization.

(2) Steam shall be introduced and penetrate into all parts of the system, and its concentration shall be maintained homogeneously. For this purpose, the system shall be well designed to facilitate the complete removal of air from the system and removal of condensate from system during the sterilization.
Note: Effective sterilisation is performed by the uniform distribution of steam to all parts of the equipment or system.

(3) Validation items required in the sterilization, such as, bioburden, and microbial challenge, and determination of lethality shall be determined. Based on this information, Steam SIP system and equipment used shall be designed and installed to assure the predetermined Sterility Assurance Level.
In addition to these validations, sterilization operational procedures shall be established and followed to keep the speading of steam in the system homogenious. Effective sterilization condition shall be maintained. For this purpose, the steam shall be homogeneously introduced and allowed to penetrate into all parts of the system.. This shall be maintained throughout the sterilization cycle period. During sterilisation, condensate shall be removed via drains from all low points in the system to ensure effectiveness of the sterilisation process.
All operational procedures shall be established as written procedures and shall be strictly followed.

(4) Followings are essential items in Steam SIP operation:
(a) Condensate shall be removed via drains, traps or bleeds from all low points in the system.
(b) Surface to be sterilized must be clean before the start of the sterilization,
(c) Steam should be continuously introduced to the system,
(d) Maintaining the system in a sterile condition after sterilization.
(e) Precise operation either by manual or automation sequencing should be ensured.

(5) System and equipment should be designed and installed by taking following points into consideration.
(a) air in the system should be removed and displaced with saturated steam for moist heat sterilization
(b) The displacement of the air with steam is achieved by a well-designed system and strategically placed bleeds, traps or valves. Gravity displacement is generally utilized for the displacement of air with steam, though pre-vacuums can be used as well.
(c) All low points in the system must be open to ensure the complete elimination of air and condensate from the system. These locations shall remain open until a steady flow of steam and condensate is observed.

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(d) Steam is introduced and bled to prevent condensate build-up from every lower point in the system. The bleed locations may or may not have to be closed once air has been eliminated; this will be determined by the need to use the bleed for condensate removal.
(e) continuous removal of condensate throughout the exposure period is necessary,
(f) After all of cold spots of the system have reached the sterilization temperature and pressure, it is essential that all condensate continue to be removed to maintain the system at the sterilizing condition.
(g) After the sterilization cycle is over, a gas (usually air or nitrogen) is introduced through a sterilizing grade filter into the system, while the total system is still under positive pressure. The gas serves to purge the system of steam and condensate, and maintain it under a slight positive pressure until ready for use. It is customary to sterilize this filter at the same time as the system.
(f) the location with the coldest temperature during the steam sterilization process is called the "cold spot".

6. Microbocidal effectiveness

6.1.Microbicidal effectiveness

.Microbicidal effectiveness studies shall:

a) demonstrate the lethal action of the sterilizing agent against a representative range of micro-organisms selected.

Note: One or more biological model systems are used for the validation of the effectiveness of the cycle. The selection of this micro-organism should be based on cycle characteristics (e.g. overkill versus bioburden based cycle) and on worst case considerations. For overkill steam sterilization cycles, spores of Bacillus stearothermophilus are recommended.

b) establish an empirical mathematical relationship defining the microbial inactivation kinetics of identified resistant micro-organisms, and confirm that the lethal action can be extrapolated to predict the probability of a micro-organism surviving after exposure to a defined treatment;
c) The D-value of the organism used to demonstrate microbicidal effectiveness when exposed to steam under specific conditions shall be known and documented.
d) select reference micro-organism(s), based on the microbial inactivation kinetics, which have a relatively high resistance to steam for use in establishing the sterilization process;
e) identify the process variables that affect the lethal action of steam and the interactions of these process variables in relation to this lethal action:
f) assess those factors that may adversely affect the delivery and/or uniform spreading of steam,
g) assess those factors that may adversely influence the effectiveness of steam based upon physical and/or chemical interactions;

NOTE : Such factors may include, for example, interactions with materials and condensate water generated from steam.

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6.2. Worst Location

The location within the system that is the most difficult to sterilise i.e. the cold spot, shall be identified. It shall be demonstrated that the SIP process is adequate to ensure sterilisation of this location to the previously determined sterility assurance level.

6.3.Test method and Criteria

The test method(s), acceptance criteria, test results and justification for the choice of
test microorganisms shall be documented.

7.Validation

7.2 Validation Protocol (cf: ICH GMP)

Prior to start validation, validation protocol shall be established.
Validation Protocol shall state how validation will be conducted and defining acceptance criteria . Validation protocol for process operation shall identify process equipment, critical process parameters/operation ranges, number of validation runs, and expected acceptance test results. Validation protocol shall contain the name of responsible person(s) of validation, execution studies, along with the time schedule. Validation shall be performed in accordance with the protocol. Any deviation from the protocol shall be discussed and investigated by the responsible and related person(s).

7.2. Installation qualification

7.2.1 Equipment

7.2.1.1 The complete specification of all equipment used to perform Steam SIP and deliver the Steam, including any ancillary items, shall be established and documented.
It shall be verified that the equipment conforms to this specification

7.2.1.2 The operating procedures for the equipment shall be ESTABLISHED and documented. These operating procedures shall include but not 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 be taken;
c) housekeeping, CALIBRATION and maintenance instructions;
c) the means by which the error in the result of a measurement for control, indication and recording can be identified;
e) details of contacts for technical support.

7.2.2 Installation

7.2.2.1 The specification for the location in which the equipment is installed shall be ESTABLISHED and documented and include but not limited to:

a) the location and the environment in which the equipment is to be installed;

b) the services that are required for the Steam SIP and for the area in which the Steam SIP system is installed;

c) the material for the construction for the parts that transport the Steam to the Steam SIP system.

7.2.22 Instructions for the installation of the equipment shall be documented, and conformity to them shall be demonstrated.

7.2.2.3 The CALIBRATION of all MEASURING CHAINS (including any test instruments) used for monitoring, controlling, indicating or recording shall be confirmed.

NOTE Alternatively, CALIBRATION may be confirmed at the commencement of OPERATIONAL QUALIFICATION.

7.2.2.4 Conformity with the specifications for the Steam SIP system installation; the area in which it is installed and the services delivered to the sterilized equipment by Steam SIP shall be ESTABLISHED.

7.3 Operational qualification

7.3.1 OPERATIONAL QUALIFICATION shall demonstrate that the installed equipment is capable of delivering the specified Steam SIP system within defined tolerances

7..3.2 Before and after each sequence of tests the CALIBRATION of test instruments shall be confirmed.

7.3.2.3 The error in the result from each MEASURING CHAIN fitted to the Steam SIP system (control, indication and recording) shall be determined at significant parts of the SIP process.

7.3.4 Data shall be generated to verify that the defined sterilizing condition of time, temperature, pressure of steam, its distribution, and sterilization assurance level are attained within specified tolerances in the Steam SIP system. This shall be identified by determining the worst location of making clean in the SIP system.

7.3.5 The number and locations of sensors, such as sensors of temperature and pressure for OPERATIONAL QUALIFICATION shall be specified. Documented evidence shall be provided to show that the number and locations are sufficient to demonstrate that requirements for sterilization in the Steam SIP system.

7.4 Performance qualification

7.4.1 Data generated during INSTALLATION QUALIFICATION and OPERATIONAL QUALIFICATION shall be valid before PERFORMANCE

QUALIFICATION is started.

7.4.2 PERFORMANCE QUALIFICATION shall ESTABLISH

— the manner of presenting for STERILIZATION including its location and orientation in the system.

— the attainment of the defined sterilization conditions throughout the Steam SIP operation cycle.

— the correlation between the measurements obtained from the instrumentation fitted to the sterilized system and the sterilizing conditions in major parts of the system.

7.4.3 PERFORMANCE QUALIFICATION shall include a comparison and evaluation of process parameters measured in the Steam SIP PROCESS to those provided at the time of designing the Steam SIP system. The acceptability of any deviation from those specified at the time of design shall be confirmed by reference to existing data, test.

7.4.4 Before and after each sequence of tests the CALIBRATION of test instruments shall be confirmed.

7.4.5 Documented evidence shall be provided to show that the number of sensors for critical parameters for PERFORMANCE QUALIFICATION are sufficient to demonstrate compliance with the specification for sterilization and within the tolerance limit.

7.4.6 If BIOLOGICL INDICATOR or INNOCURATED CARRIERS are used during the PERFORMANCE QUALIFICATION, they shall comply with ISO 11138-3.

7.4.7 If CHEMICAL INDICATORS are used as a part of during the PERFORMANCE QUALIFICATION, they shall comply with ISO 11138-3.4,5.

7.4.8 If in addition to the measurement of physical parameters, the STERILIZATION PROCESS is to be based on BIOBURDEN, microbiological PERFORMANCE QUALIFICATION studies shall be done with the cycle variables set to the least favorable limit. The outcome of such studies shall predict that on application of the SIP PROCESS, the specified requirements for STERILITY will be met.

7.4.9 PERFORMANCE QUALIFICATION shall include a series of at least three consecutive and successful exposures of product to the Steam SIP PROCESS to demonstrate the reproducibility of the process. A successful exposure shall be determined by the measurement of physical parameters which shall be determined by the intended sterility assurance level.

NOTE If failure can be attributed to factors not relevant to the effectiveness of the Steam SIP PROCESS being validated, this test may be documented as unrelated to performance of the Steam SIP PROCESS without requiring three further consecutive, successful runs.
Examples of this type of failure include, but are not limited to, power failures, loss of SERVICES, or failure of external monitoring equipment.

7.5 Review and approval of validation

7.5.1 Information gathered or produced during INSTALLATION QUALIFICATION, OPERATIONAL QUALIFICATION and PERFORMANCE QUALIFICATION shall be documented and reviewed for conformity to the acceptance criteria specified for each element of the VALIDATION process. The results of this review shall be documented.

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7.5.2 A complete process specification, including the PROCESS PARAMETERS and their tolerances shall be confirmed. This process specification shall also include the criteria for designating the Steam SIP PROCESS used for a maximum LOAD for contaminant as conforming.

8. Revalidation

(1) Revalidation of processes carried out with specified equipment shall be performed at defined intervals.

(2) Revalidation report(s) shall be documented and retained.

(3) Revalidation data shall be reviewed at least annually against specified acceptance criteria in accordance with documented procedures, and a rationale documented whether or not re-validation is required.
Revalidation should be performed unless there is sufficient data to demonstrate the continued appropriateness of the Steam SIP processes. Records of reviews of revalidation data, and corrective actions taken in the event that the specified acceptance criteria are not met, shall be retained.

9.Routine Control: Refer to Part 4-2, section 5. Routine Control

10.Change Control: Refer to Part 4-2, section 5. Change Control

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Secretariat of ISO/TC 198/WG 9 **Doc. ISO/TC 198/WG 9 N 152**

our date 2001-12-18 our reference stt-dga

your date your reference

To the Members of

ISO/TC 198/WG 9

"Aseptic processing of health care products"

Informative Annex to ISO 13408-4 and ISO 13408-X "Schematic examples of CIP and SIP" for inclusion in the revised drafts on CIP and SIP

Informative Annex on "Necessary items to be generally considered for the application of SIP by using various kinds of sterilant" for inclusion in the revisal draft on SIP

from Dr Kawamura

NOTE The papers attached have been tabled at the last meeting of ISO/TC 198/WG 9 in Cologne. It was agreed that these papers be considered during the preparation of the revised working drafts on CIP and SIP. Dr Kawamura kindly offered to prepared revised drafts on CIP and SIP. The revised working drafts will then be sent to the members of WG 9 for comment.

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December 10,2001

Informative Annex to ISO 13408-6, CIP,SIP, and Steam SIP

Drafted by Dr. K.Kawamura

Part 1: Schematic examples of CIP and SIP, which show the same equipment is subjected to CIP and SIP

Part 2: Necessary items to be generally considered for the application of SIP by using various kinds of sterilant

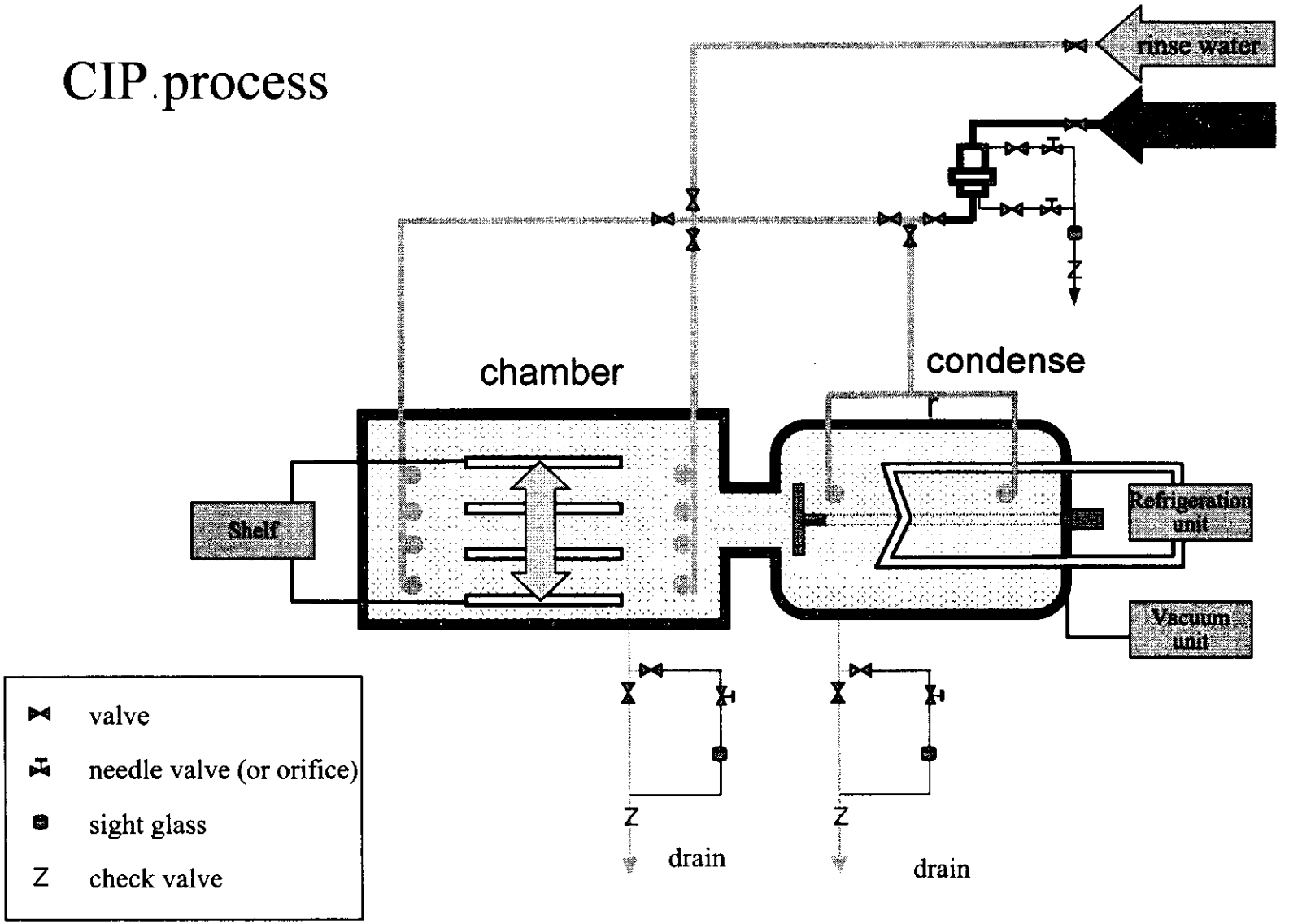
Part 2: Necessary items to be generally considered for the application of SIP by using various kinds of sterilant

1. Determination of the assembled equipment group to be sterilized be SIP
2. Selection of sterilant
3. Effectiveness of sterilant
4. Determination of the concentration of the sterilant to be used
5. Compatibility of the sterilant
6. Development of determination mehotd of the sterilant concentration,
   - including temperature and pressure in case of steam sterilization
7. Target of sterilization – e.g. SAL 10^{-6}
8. Determination of impurities and/or degradation product which affect the

sterilization- including e.g. condensed water

9. Determination of elimination method of impurities or degradation product from the system
10. Total equipment design by which introduction of sterilant and exhausting the degradation or condensed water
11. Selection of measuring equipment to determine the process parameters
12. Calibration of measuring equipments
13. Selection of process parameters
14. Test runs and confirmation of sterilization condition
15. Determination and confirmation of sterilization completeness by BI and physico- -chemical measures- including the homogeneity of sterilant within the system
16. Determination of process parameters
17. Determination of monitoring method and periodical check and review items
18. Establishment of SOP
19. Training and education for operators
20. Follow

CIP process



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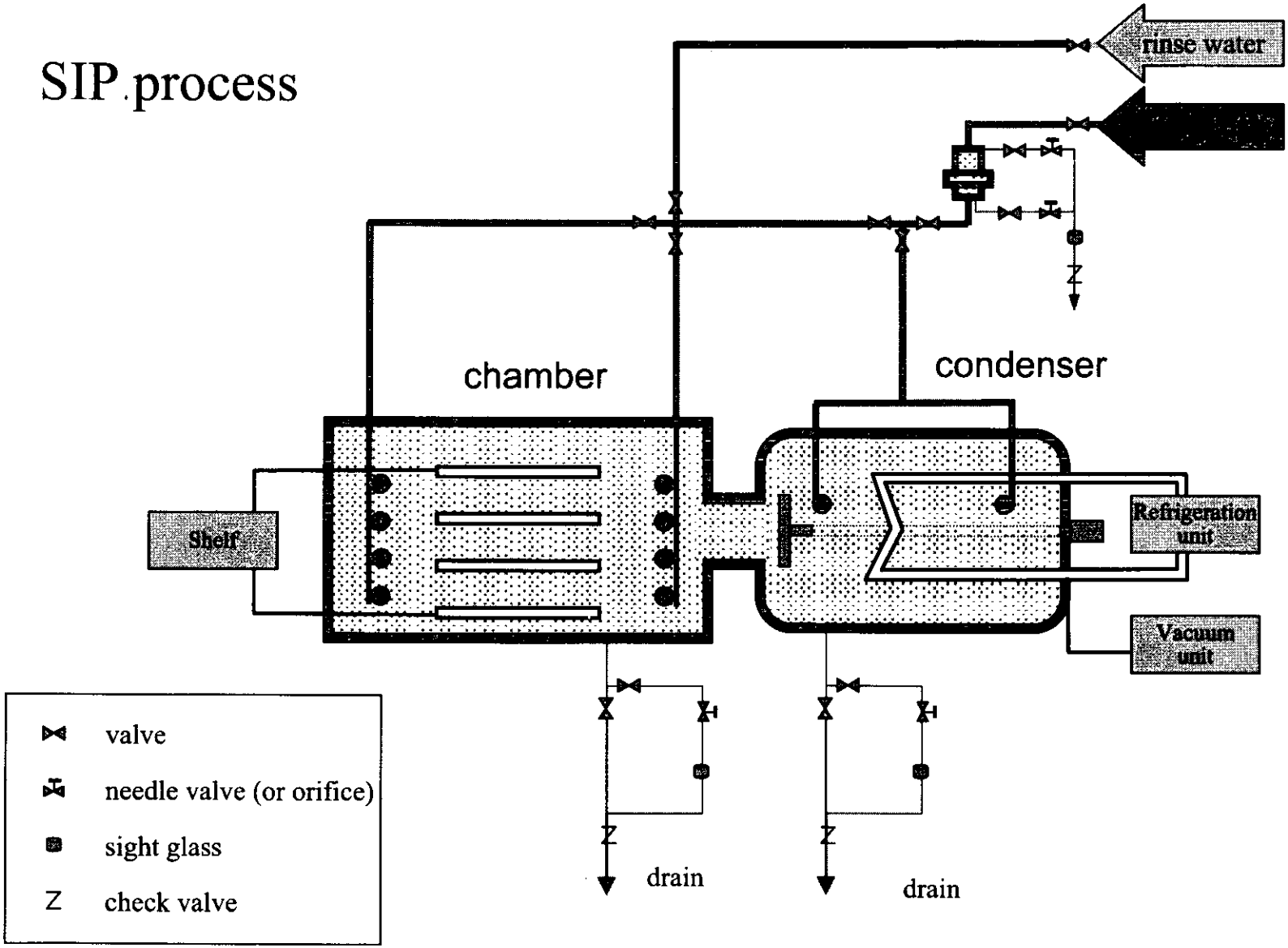
SIP process



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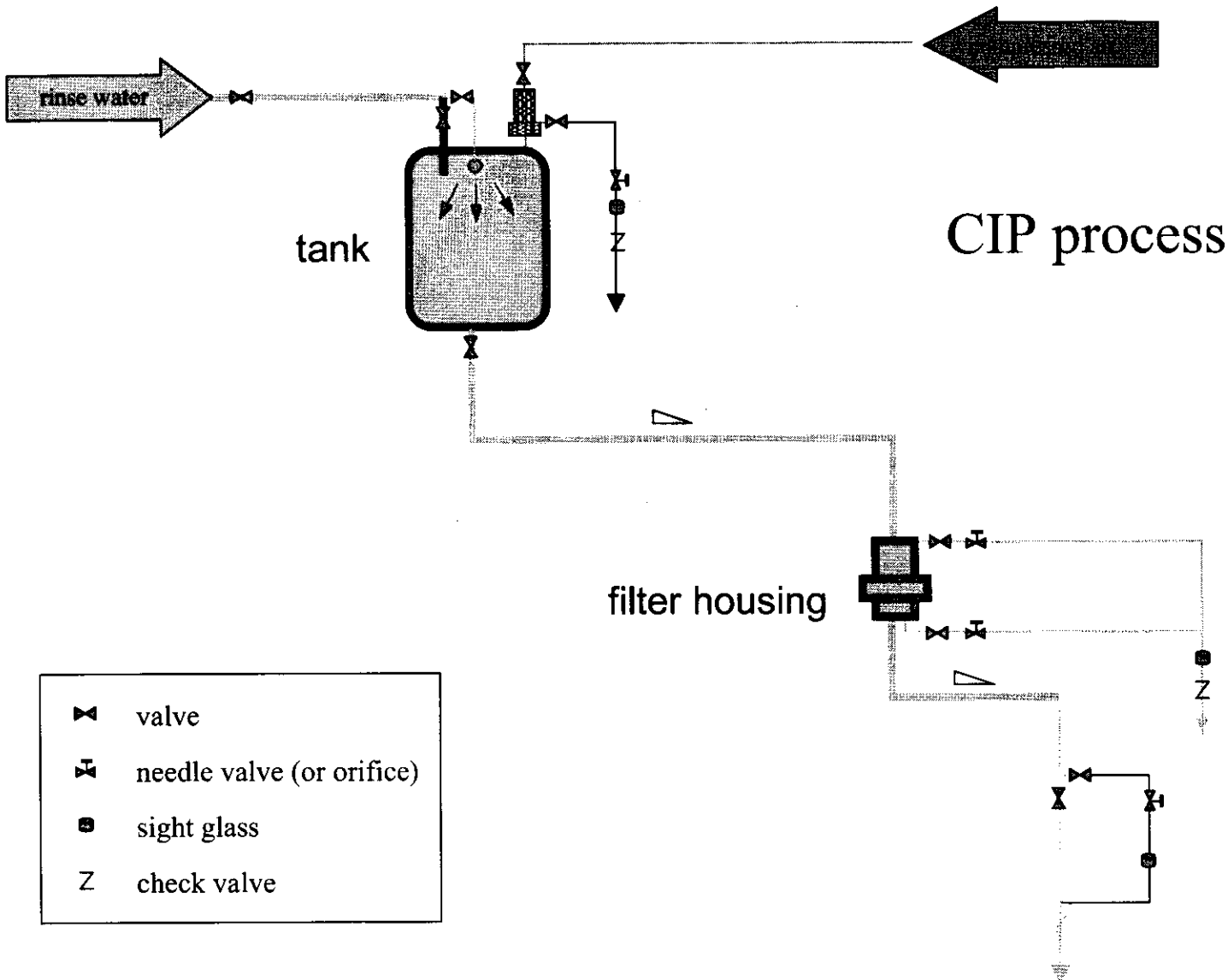

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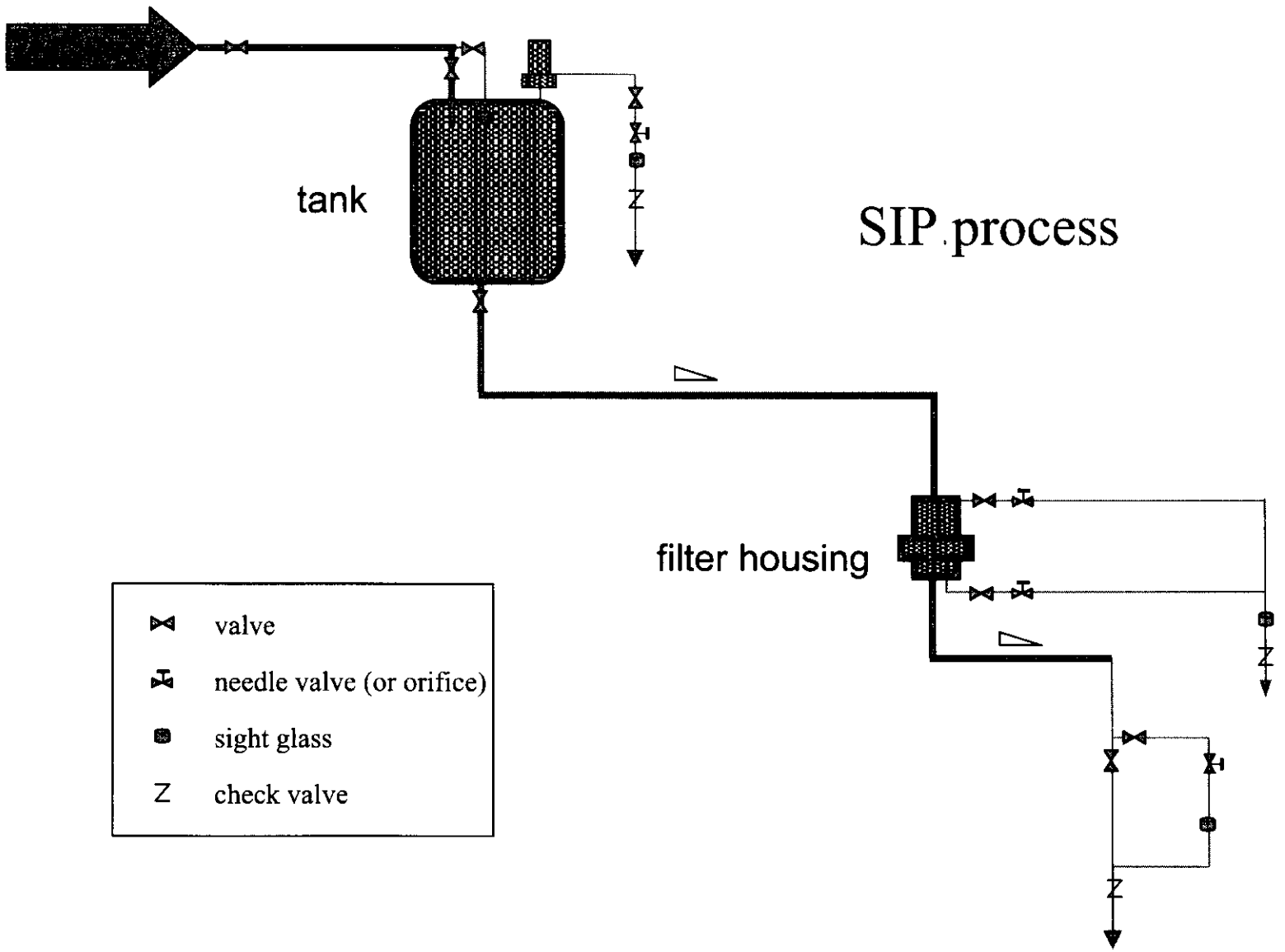

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