

INTERNATIONAL STANDARD

ISO
13408-1

First edition
1998-08-01

Aseptic processing of health care products —

Part 1: General requirements

*Traitement aseptique des produits de santé —
Partie 1: Exigences générales*



Reference number
ISO 13408-1:1998(E)

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Printed in Switzerland

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.

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.

International Standard ISO 13408-1 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: *Filtration¹⁾*
- Part 3: *Freeze-drying*
- Part 4: *Sterilization and cleaning in place¹⁾*
- Part 5: *Aseptic processing of solid medical devices*
- Part 6: *Isolator/barrier technology*

Annexes A and B of this part of ISO 13408 are for information only.

1) ISO 13408-1 includes normative and informative clauses on these subjects until such time that the more detailed additional parts of ISO 13408 are approved and published. Once such approved International Standards exist, it is intended that the related clauses included in ISO 13408-1 be deleted.

Introduction

Health care products that are labeled "sterile" have to be prepared using appropriate and validated methods. ISO/TC 198 has prepared standards for terminal sterilization of health care products by irradiation (ISO 11137), by moist heat (ISO 11134), by liquid chemical sterilants (ISO 14160) and by ethylene oxide (ISO 11135). When a health care product is intended to be sterile and cannot be terminally sterilized, aseptic processing provides an alternative. There are two distinct situations in which aseptic processing is applied:

- a) the aseptic preparation and filling of solutions;
- b) the aseptic handling, transfer and packaging of solid products which cannot be terminally sterilized in their final containers.

Aseptic processing requires the presterilization of all product parts or components that are in direct contact with the aseptically filled product. The product is processed in a controlled environment in which microbial and particulate levels are maintained at defined levels and where human intervention is minimized.

Aseptic processing is an exacting and demanding discipline. Manufacturers use validated systems, adequately trained personnel, controlled environments and well-documented systematic processes to assure a sterile finished product.

While terminal sterilization involves the use of a process of known lethality, the assurance of sterility associated with aseptic processing can only be inferred as facilities, equipment and people are all factors associated with the process. Product development data should also exist to support the maintenance of sterility by the container and/or closure system following aseptic production.

The major elements to be considered in aseptic processing include:

- a) training of personnel;
- b) layout and specifications for buildings, equipment and facilities;
- c) particulate and microbial environmental monitoring programmes;
- d) systems for water, steam, air and other process gases;
- e) descriptions of and procedures for manufacturing operations including people, materials, material flow, solution preparation and associated acceptance criteria;
- f) use and validation of sterilization processes, including disinfection practices;
- g) validation methods and data requirements for media fills and container/closure systems;
- h) operating practices for acceptance criteria, investigation reviews and release/reject decisions.

Aseptic processing of health care products —

Part 1: General requirements

1 Scope

This part of ISO 13408 specifies the general requirements for, and offers guidance on, processes, programmes and procedures for the validation and control of aseptically processed health care products.

This part of ISO 13408 includes requirements and guidance relative to the overall topic of aseptic processing.

NOTE Future parts of ISO 13408 will address specialty topics related to aseptic processing, including detailed descriptive information concerning various specialized processes and methods related to filtration, freeze-drying, sterilization in place, cleaning in place, isolator technology, and solid medical devices.

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 in particular to national or regional jurisdictions.

2 Definitions

For the purposes of this part of ISO 13408, the following definitions apply.

2.1

action level

(environmental monitoring) established microbial or particulate level requiring immediate follow-up and corrective action if exceeded

2.2

action level

(media fill) established level or number of positive media-filled units, requiring investigation of cause and definitive corrective action if exceeded

2.3

alert level

(environmental monitoring) established microbial or particulate level giving early warning of potential drift from normal operating conditions which is not necessarily grounds for definitive corrective action but which could require follow-up investigation

2.4

alert level

(media fill) established level or number of positive media-filled units, the cause of which should be investigated, but which is not necessarily grounds for definitive corrective action

2.5
aseptic filling

part of aseptic processing where a presterilized product is filled and/or packaged into sterile containers and closed

2.6
aseptic filling line

manufacturing structure or arrangement where product containers and/or devices are aseptically filled

NOTE Generally, the aseptic filling line is arranged to permit the filling of product containers and/or devices in a linear manner; hence the term "line".

2.7
aseptic processing

handling the aseptic filling of product containers and/or devices in a controlled environment, in which the air supply, materials, equipment and personnel are regulated to control microbial and particulate contamination to acceptable levels

2.8
aseptic processing area
APA

controlled environment for aseptic processing, consisting of several zones, in which the air supply, materials, equipment and personnel are regulated to control microbial and particulate contamination to acceptable levels

2.9
batch manufacturing record

process documentation that supports the manufacturing of a lot or batch of product consistent with defined product manufacturing and quality assurance specifications

2.10
bioburden

population of viable microorganisms on or in a health care product or package prior to sterilization

2.11
bioburden

population of viable microorganisms on materials and equipment introduced into the APA

2.12
biological indicator

microorganism, traceable to a recognized culture collection and of a known sterilization resistance, that is used to develop and/or validate a sterilization process

NOTE The microorganisms are frequently used with a carrier, which is the supporting material on which test organisms are deposited.

2.13
container configuration

denotes the same container design independent of capacity

NOTE Since all aseptically processed products may not be final-filled into a container, this part of ISO 13408 also uses the expression "product/container configuration."

2.14
critical processing zone

locality of aseptic processing area in which product and product contact surfaces are exposed to the environment

NOTE Aseptic manipulations performed in a critical processing zone can include aseptic connections, filling, stoppering and closing operations.

**2.15
critical surface**

surface in the critical processing zone within close proximity to aseptic operations and which poses a potential risk to the product

**2.16
differential air pressure**

difference in pressure between or within rooms or areas

**2.17
disinfectant**

chemical or physical agent that inactivates vegetative microorganisms but not necessarily highly resistant spores

**2.18
environmental flora**

environmental isolates

microorganisms present in and/or isolated from processing or manufacturing environments

**2.19
gas filter**

porous material placed in compressed gas lines to remove nonviable and/or viable particulate matter from gas streams which come directly or indirectly in contact with a product

**2.20
health care product**

medical device, medicinal product (pharmaceuticals and biologicals) and *in vitro* diagnostics

**2.21
high efficiency particulate air filter**

HEPA filter

retentive matrix having a minimum particle-collection efficiency of 99,97% (that is, a maximum particle penetration of 0,03%) for 0,3 µm particles of thermally generated DOP or specified alternative aerosol

**2.22
laminar air flow**

air flow which is comprised of uniform velocities of air flow along parallel flow lines

NOTE Laminar air flow is frequently used in cabinets and hoods.

cf. **unidirectional air flow** (2.33)

**2.23
media fill**

method of evaluating an aseptic process using a microbial growth medium

NOTE Media fills are understood to be synonymous to process simulation tests, simulated product fills, simulated filling operations, broth trials, broth fills, etc.

**2.24
other processing zone**

processing zone, other than critical processing zones, in which health care products are not exposed to the environment

NOTE These zones include staging, transport and storage areas for sterilized components, containers and bulk products in protected vessels; autoclave-unloading areas; and processing rooms from which critical areas are accessed.

**2.25
product contact surface**

surface which comes into contact with sterilized product or containers/closures

2.26**product sterilizing filter**

porous material with a nominal rating of less than or equal to 0,22 μm , capable of retaining a defined number of microorganisms using defined challenge tests and conditions

2.27**qualification**

documented scientific process used by the health care product manufacturer to assure the reliability and capability of equipment and/or processes before approval for use in manufacturing

NOTE Qualification of equipment and/or processes generally includes installation qualification, operational qualification, and performance qualification.

2.27.1**installation qualification**

process which demonstrates that the unit or process under test is in compliance with all relevant design criteria and safety standards, and is calibrated

2.27.2**operational qualification**

testing which demonstrates that the equipment and/or process functions as intended, that procedures exist describing operation of the equipment, and that personnel have been trained to set up, operate and maintain the equipment

2.27.3**performance qualification**

testing which involves actual challenges to the system to substantiate its effectiveness and reproducibility

2.28**shift**

scheduled period of work or production, usually less than 12 h, staffed by a single defined group of workers

2.29**sterile**

state of being free from viable microorganisms

NOTE In practice, no such absolute statement regarding the absence of microorganisms can be proven.

cf. **sterilization** (2.30)

2.30**sterilization**

validated process used to render a product free from viable microorganisms

NOTE The number of microorganisms that survive a sterilization process can be expressed in terms of probability. While the probability may be reduced to a very low number, it can never be reduced to zero.

2.31**support area outside the APA**

environmentally controlled area not within the aseptic processing area and not part of critical or other processing zones

2.32**terminal sterilization**

process whereby a product is sterilized in its final container and which permits the measurement and evaluation of quantifiable microbial lethality

2.33**unidirectional air flow**

air flow which has a singular direction of flow and may or may not contain uniform velocities of air flow along parallel flow lines

cf. **laminar air flow** (2.22)

2.34 vent filter

porous material capable of removing viable and nonviable particles from gases passing in and out of a closed vessel

3 Quality management systems

A quality management system, appropriate to the nature of the operations, shall be implemented to assure control over all activities affecting aseptic processing. Unless a superseding national, regional, or international Good Manufacturing Practice (e.g. the World Health Organization GMPs) is employed, the quality management system should be in conformance with the requirements of ISO 9001, and/or ISO 9002.

NOTE 1 Guidance on selecting a suitable model is given in ISO 9000-1.

NOTE 2 The quality management system may include, in addition to the product, components and process specifications, written procedures and specifications for:

- a) environmental conditions in the aseptic processing area (APA);
- b) cleaning and disinfection of the APA;
- c) sterilization of the product, equipment, and container/closure system;
- d) aseptic processing of bulk products, e.g. freeze-drying, aseptic crystallization, powder drying, etc.;
- e) introduction of items into the aseptic processing area or critical processing zone;
- f) employee gowning practices;
- g) in-process testing and evaluation;
- h) operator and technician training;
- i) change control practices;
- j) validation.

4 Personnel

4.1 Personnel management

4.1.1 Documented procedures for aseptic processing operations, personnel training, and assessment of personnel performance against defined criteria, shall be established and implemented.

4.1.2 The effectiveness of the defined procedures shall be evaluated at defined intervals.

4.1.3 Management shall be responsible for the training required to qualify individuals for access to the APA as defined in 4.2

4.2 Training for APA qualification

4.2.1 All personnel entering the APA shall be qualified based on successful training as described in 4.2.2 and 4.2.3. Training in the various disciplines and activities should be in proportion to the individual's duties and directed at the appropriate level of knowledge.

4.2.2 Personnel compliance issues shall be included in the employee training program. All personnel working in the APA, including supervisors and maintenance staff, shall be trained with reference to:

- a) personal hygiene, e.g. hand washing and disinfection procedures;
- b) rules concerning the wearing of cosmetics or jewelry;
- c) aseptic technique; e.g. employees working in the APA shall avoid
 - 1) unnecessary movement and contact with critical surfaces;
 - 2) unnecessary movements and talking which can generate particles or create turbulence;
 - 3) reaching across open containers and exposed product and components, and
 - 4) blocking air flow over critical surfaces.
- d) fundamentals of microbiology;
- e) gowning procedures (see clause 9);
- f) manufacture of sterile products within the APA;
- g) emergency procedures to protect product quality, e.g. loss of HVAC system, loss of power, etc.

4.2.3 Other personnel, including management and other QA/QC personnel, who require temporary access to the APA shall be accompanied at all times by a person trained and qualified in accordance with 4.2.2 and shall be trained in the essential elements of:

- a) personal hygiene;
- b) rules concerning the wearing of cosmetics or jewelry;
- c) essential elements of aseptic technique;
- d) fundamentals of microbiology;
- e) gowning procedures.

If, because of special constraints of the APA in question, this is impractical, these staff should be closely observed by experienced staff.

4.2.4 Records of training and evaluation shall be maintained.

4.2.5 All personnel that directly participate in the filling or manufacture of sterile products in the critical processing zones shall have taken part in a media fill that meets the requirements of this part of ISO 13408 at least once per year.

4.2.6 New personnel working in the critical processing zone shall take part in at least one actual media fill, or equivalent aseptic operations which may be performed in a training environment, before being permitted to participate in processes carried out in critical process zones.

4.2.7 All personnel shall be retrained, in accordance with documented procedures, on both job functions and relevant quality systems elements at a defined frequency, and if there is an indication of necessity.

4.3 General employee health

4.3.1 Personnel shall be required to report conditions which may affect aseptic work such as fever, skin lesions, common cold, diarrhoea, etc.

4.3.2 Personnel with reported health conditions affecting aseptic work shall not be permitted to enter the critical processing zones, but may be assigned work in other areas.

NOTE Initial and periodic medical examinations should be performed for individuals assigned to aseptic processing operations.

4.4 Monitoring of personnel

4.4.1 Employees trained and qualified to work in the APA shall be subject to a defined microbiological monitoring programme that includes the sampling of items such as garments and gloves.

NOTE It is general practice to conduct microbiological sampling of personnel garments and gloves after use.

4.4.2 Results of the monitoring programme shall be used to identify trends and evaluate the need for retraining.

5 Facility design

5.1 Facility design features

Layout and construction features which shall be considered in the design of an APA include:

- a) wall, floor and ceiling surfaces which can be cleaned readily and which can withstand cleaning agents and disinfectants;
- b) ceilings which are effectively sealed;
- c) avoidance of ledges and other horizontal surfaces which can collect particles or disturb air flow;
- d) installation of pipes, ducts, and other utilities in a manner that avoids recesses and other surfaces which are difficult to clean;
- e) adequate space for gowning areas, garment storage, soiled garment disposal, hand washing and disinfection;
- f) separation of gowning and preparation areas from the APA by means of airlocks and pass-through windows for components, supplies and equipment;
- g) air flow patterns which could affect products and critical surfaces;
- h) windows or other means of observing aseptic procedures, where appropriate;
- i) maintenance and monitoring of appropriate differential air pressure;
- j) airlocks equipped with a system to avoid simultaneous opening of doors;
- k) maintenance of temperature and, if necessary, relative humidity within defined tolerances and, if possible, monitored continuously;
- l) layout of equipment in the APA to facilitate operator and maintenance personnel access while minimizing exposure of open containers or product;
- m) location of equipment requiring frequent operator intervention or maintenance remote from critical processing zones;
- n) potential for cross-contamination sources.

NOTE 1 The location of the APA relative to other areas within a manufacturing facility should be given full consideration, and the rationale for its location should be documented.

NOTE 2 In multipurpose facilities, the APA should be located away from high traffic areas (materials, equipment and personnel) or separated by physical barriers.

NOTE 3 Appropriate facility design should be considered when sensitizing agents, cytotoxics or other hazardous materials are processed within the APA.

5.2 Facility design review

5.2.1 A facility design review procedure shall be conducted and documented to demonstrate that the facility design is consistent with product specific requirements. A facility design review shall also be applied when introducing new processes or product types.

5.2.2 This requirement shall be applied retrospectively to existing facilities.

5.3 Material flow

Aseptic processing facilities shall be designed to promote a controlled flow of components and materials in order to:

- a) maintain the microbiological integrity of critical processing zones;
- b) minimize the entry of contamination from outside the APA, and contain any such contamination so it does not reach critical processing zones; and
- c) prevent mingling of clean and dirty items.

6 Aseptic Processing Area (APA)

6.1 General

NOTE The APA consists of zones which require separation and control. The specification for air quality in each zone depends on the nature of the operation being carried out. These zones are the critical processing zones and other processing zones.

6.1.1 The APA shall be a controlled environment such that microbial and particulate contamination are maintained within specified limits.

6.1.2 Access to APA shall be restricted to qualified personnel as described in 4.2.

6.1.3 Sufficient unidirectional air flow and/or positive differential air pressure shall exist to prevent contamination of the critical processing zone and APA from adjacent areas.

6.1.4 An environmental monitoring programme shall be established, documented, implemented and maintained (see clause 14).

6.2 Critical processing zones

6.2.1 Critical processing zones shall be identified, and microbial and total particulate specifications shall be documented.

6.2.2 Appropriate measures shall be taken to minimize the potential for contamination of sterilized items, materials or the environment.

6.2.3 Critical processing zones shall contain less than 3 500 particles of diameter equal to or larger than 0,5 µm for each cubic metre of air as measured during operational conditions.

NOTE 1 This quality of air is commonly referred to as Grade A, Class M 3.5, or Class 100 in existing, commonly-used national and international air quality standards.

NOTE 2 Critical processing zones should be subject to effective monitoring during operations to identify trends in environmental data.

NOTE 3 It is accepted that it may not always be possible to demonstrate conformity with particulate standards at the point of fill when filling is in progress, due to the generation of particles or droplets from the product itself.

6.2.4 Critical processing zones shall be routinely monitored for the presence of microorganisms, i.e. environmental flora/isolates (14.3.1.1) and airborne particles (14.4).

6.3 Other processing zones

6.3.1 Other processing zones shall be identified, and microbial and total particulate specifications shall be documented.

6.3.2 Appropriate measures shall be taken to minimize the potential for contamination of sterilized items, materials or the environment.

6.3.3 Other processing zones shall contain less than 350 000 particles of diameter equal to or greater than 0,5 µm for each cubic metre of air as measured during operational conditions.

NOTE This quality of air is commonly referred to as Grade B, Class M 5.5 or Class 10 000 in existing, commonly used national and international air quality standards.

6.3.4 Other processing zones shall be routinely monitored for the presence of microorganisms, i.e. environmental flora/isolates (14.3.1.1) and airborne particles (14.4).

7 Support areas outside the APA

7.1 Support areas shall contain less than 3 500 000 particles of diameter equal to or greater than 0,5 µm for each cubic metre of air as measured during operational conditions.

NOTE 1 This quality of air is commonly referred to as Grade C/D, Class M 6.5 or Class 100 000 in existing, commonly used national and international air quality standards.

NOTE 2 The disinfection and environmental monitoring of this area may be less frequent than that utilized for the processing zones.

7.2 Support areas shall be monitored routinely for the presence of microorganisms, i.e. environmental flora/isolates.

8 Environmental air systems and controls

NOTE The basic elements of environmental air systems and control programmes should consider proper design and control of the aseptic processing facilities including: relative humidity, temperature, air velocity, HEPA filtration, direction of airflow, and room-to-room differential air pressure.

8.1 Temperature and humidity

8.1.1 Temperature and, if necessary, humidity levels shall be specified, controlled, maintained and monitored to assure employee comfort while maintaining product attributes, as this has a direct impact on aseptic techniques and the potential level of contamination.

8.1.2 These requirements shall be met with a full complement of operational personnel and with all equipment in operation.

8.2 Air

8.2.1 Differential air pressure shall be specified, controlled, and monitored between zones.

8.2.2 All critical processing zones shall receive HEPA filtered air that has a velocity sufficient to maintain the required zone classification.

8.2.3 Where unidirectional air flow is specified, velocities shall be monitored for each HEPA filter according to a programme at established intervals.

NOTE Significant reductions in velocity can increase the possibility of contamination.

8.2.4 Air flow patterns shall be determined and documented to demonstrate that air flow is appropriate to the process being performed and shall include investigations into the effects of turbulence on the sweeping action of the air.

8.3 HEPA filter integrity

8.3.1 Certification

HEPA filters shall be accompanied by a supplier's certification of efficiency.

8.3.2 Initial and periodic testing

8.3.2.1 Upon installation, filters shall be integrity-tested by a suitable method.

8.3.2.2 When conditions are being maintained through the use of HEPA filters, the filters shall be tested for integrity within the facility and certified as measured by a suitable test, e.g. paraffin oil, chemical aerosol challenge such as DOP, etc.

8.3.2.3 The velocity of air flow through the filters shall be tested at specified intervals.

8.3.2.4 Air flow patterns shall be reconfirmed whenever an air flow configuration change has been introduced.

8.3.2.5 Filters shall be tested according to documented procedures when events or situations that might affect the integrity of the filter have occurred, or environmental monitoring results suggest that the integrity of the filter may have been compromised.

8.3.3 Filter failure

8.3.3.1 In the event of filter failure, a documented investigation shall be conducted to identify the potential cause of the failure, and any remedial action that has been taken shall be documented.

8.3.3.2 A documented management review covering the quality and disposition of potentially affected products shall be conducted in accordance with defined procedures.

9 Gowning

9.1 Gowning training

9.1.1 Employees shall be trained in appropriate gowning procedures to minimize the introduction of contamination into the APA.

9.1.2 Effectiveness of training for gowning procedures shall be verified using microbiological methods.

NOTE Total particle methods may also be used to show effectiveness of gowning.

9.1.3 Results of verification of gowning training shall be communicated to employees.

9.2 Gowning requirements

9.2.1 Personnel shall wear dedicated factory clothing, including shoes, prior to entering the gowning area.

NOTE 1 Personnel should enter the gowning area by way of an airlock.

NOTE 2 Personnel may change into dedicated factory clothing in the airlock adjacent to the gowning area.

9.2.2 Personnel in support areas shall wear garments which meet the particulate requirements specified for the area.

NOTE A mesh hair net and beard cover, if required, are donned in the airlock. Disposable shoe covers may be used in addition to dedicated shoes.

9.2.3 Personnel entering the APA shall wear garments that are processed to render them free from viable microorganisms and that minimize particle generation.

NOTE 1 Sterile, flexible goggles are often worn over the hood to cover the eyes and eyebrows. Care must be taken to assure that, at the areas where clothing meet areas such as the lower leg, wrist and neck, no gaps or exposed skin are apparent. Some cleanroom operations use arm covers, extra-high boots and double gloves to minimize the likelihood of gaps or tears occurring during movement.

NOTE 2 After a garment has been tested for microbial contamination (see 4.4), it should not be worn in the APA until cleaned.

9.3 Control of gowned personnel

9.3.1 Written procedures shall be implemented to assure that personnel do not compromise the aseptic processing environment.

9.3.2 Gloves and gowns shall be checked regularly for proper fit and integrity.

9.3.3 Operators working in support areas outside the APA shall not have access to the APA without undergoing appropriate training and gowning procedures (see 4.2).

NOTE Personnel conducting filling operations should not routinely be exchanged during a shift with employees performing other functions within the APA.

10 Cleaning and disinfection of the APA

10.1 Disinfectants and cleaning agents

10.1.1 Aseptic processing areas shall be cleaned and disinfected on a regular basis in accordance with a documented procedure.

10.1.2 Only cleaning agents and disinfecting agents which are validated and approved shall be used.

10.1.3 Disinfectants and cleaning agents shall be free of microbiological contamination.

10.1.4 Records of cleaning and disinfection shall be prepared and retained.

10.1.5 Procedures shall include use of approved agents, cleaning schedules, disinfectant application, post-disinfection cleaning if required, employee safety precautions, and care and storage of cleaning aids.

10.1.6 The removal of disinfectant and cleaning agent residuals on product contact surfaces shall be validated.

10.1.7 Disinfectants shall have a stated expiration date.

NOTE 1 Disinfectant containers should be cleaned thoroughly and, if necessary, sterilized before reuse.

NOTE 2 The manufacturers' instructions should be followed with respect to storage and use.

NOTE 3 National personnel safety regulations should be considered when selecting disinfectants and disinfectant procedures.

NOTE 4 Interchanging or rotating disinfectants should be considered due to potential changes in environmental flora/isolates.

NOTE 5 A sporicidal agent might be necessary if environmental monitoring indicates the presence of spore-forming organisms, moulds and fungi.

NOTE 6 Disinfectant and cleaning agent containers and other cleaning equipment to be used in the APA should be reserved exclusively for this area.

10.2 Validation of disinfection procedures

10.2.1 The effectiveness and frequency of the disinfection procedure shall be determined as part of the process validation.

10.2.2 Each facility shall have appropriate procedures in place to evaluate, approve and control the use of disinfectants.

NOTE Evaluation of the efficacy of disinfectants should consider the reduction of types and numbers of microorganisms recovered from surfaces during routine environmental monitoring.

10.3 Monitoring of effectiveness of cleaning and disinfection

10.3.1 The effectiveness of cleaning and disinfection shall be determined as part of an overall environmental monitoring programme.

10.3.2 When unusual microbial results are encountered or persist, an investigation to identify the source of contamination shall be performed and documented.

11 Qualification of equipment and utilities, and process validation

11.1 General

11.1.1 All processes used in the APA which affect product sterility or product attributes shall be validated.

11.1.2 Procedures shall be in place describing the operations of all critical equipment.

11.2 Qualification of processing equipment

Processing equipment such as sterilizers, component washers, filters, fillers, closure placement equipment, sealing machinery and freeze-dryers shall be qualified to assure suitability for its intended purpose.

11.3 Validation of sterilization of equipment product-contact surfaces

11.3.1 Equipment surfaces which contact product shall be sterilized.

11.3.2 Sterilization processes applied to the above equipment surfaces shall be validated.

11.4 Validation of process-related utilities

Process-related utilities such as purified water, water-for-injection, pharmaceutical compressed air (and/or other gases), clean or water-for-injection steam, and clean-in-place/steam-in-place systems shall be validated to be suitable for intended use.

12 Materials and equipment delivered to aseptic areas

12.1 Sterilization

Each of the sterilization processes used to sterilize components or materials used in the aseptic suite shall be independently validated.

12.2 Gases

12.1.1 All compressed gases that contact products, container/closures or product contact surfaces shall be sterilized.

12.2.2 Compressed air shall be controlled for moisture and oil contamination.

12.3 Bioburden

The characterization and resistance to microbial inactivation of the bioburden on components and equipment that are to be introduced into the APA shall be periodically determined.

12.4 Depyrogenation

When a depyrogenation process is used, data shall demonstrate that the process will remove a greater quantity of endotoxin than might have been originally present in the component or product.

NOTE 1 Data should be available that demonstrate a knowledge of the quantity of endotoxin on materials prior to treatment in a depyrogenation process.

NOTE 2 Plastics medical devices and/or containers may be depyrogenated by rinse processes, and/or high temperature moulding, and/or extrusion processes prior to filling. These items should be sterilized as soon as possible after the washing process to prevent endotoxin contamination.

NOTE 3 Rubber compound stoppers may be rendered pyrogen-free by multiple cycles of washing and rinsing prior to final steam sterilization.

13 Processing time

13.1 The compounding of bulk solutions shall be controlled in order to prevent potential increase in microbiological levels, and possibly endotoxins, that can occur up to the time that the bulk solutions are sterile filtered.

NOTE Solutions should be compounded in a support areas (see 7.1) in sealed tanks, particularly if the solution is to be stored prior to filtration.

13.2 The total time for the product filtration and filling operations, and holding time after filtration and prior to filling, shall be limited to a defined maximum.

NOTE Elapsed time between component washing and sterilizing should be minimized and limited to a defined maximum.

13.3 Written documentation shall exist that describes the operational procedures for the handling and processing of materials and equipment delivered to aseptic areas.

14 Environmental monitoring programmes

NOTE The environmental monitoring programme is a defined, documented programme that describes the routine particulate and microbiological monitoring of processing and manufacturing areas and includes a corrective action plan when action levels are exceeded.

14.1 Procedures

14.1.1 Procedures describing the environmental monitoring programme shall be established, documented and maintained.

14.1.2 These procedures shall describe:

- a) frequency of monitoring;
- b) type of monitoring;
- c) sites monitored;
- d) alert and action levels; and
- e) actions taken when specifications are exceeded.

14.2 Sampling

14.2.1 Processing zones and frequency of sampling

14.2.1.1 Product contact and material contact sites in the critical processing zone shall be monitored during and/or immediately after completion of the filling operation.

14.2.1.2 Sampling in critical processing zones shall be performed in a manner which presents a minimal contamination risk to the product.

14.2.1.3 Other processing zones shall be monitored at a defined frequency based on classification of the zones and testing data.

14.2.1.4 Support areas outside the APA shall be monitored at a defined frequency, but may be monitored less frequently than processing zones.

14.2.1.5 The frequency of such monitoring for different facilities shall be based on historical environmental monitoring data and the type of product and process.

14.2.2 Sampling sites

Sampling sites should be derived from and consistent with those used during validation activities.

NOTE The individual sampling sites for each programme should be at the discretion of the manufacturer, reflecting differences in facility/equipment design and processing parameters.

14.3 Microbiological environmental monitoring programme

14.3.1 General

14.3.1.1 The aseptic processing area shall be routinely monitored for the presence of microorganisms, i.e. environmental flora/isolates. Periodic monitoring shall include methods for yeast, moulds and other microorganisms.

14.3.1.2 Validated recovery methods and calibrated equipment shall be used.

14.3.1.3 Samples shall be collected from areas in which components and product are exposed to the environment, such as critical processing zones and filling lines.

14.3.1.4 Additional microbial and particulate monitoring shall be performed following start-up of operations or following periods of extended shut-down or modifications to the facility.

14.3.1.5 Gases which are sterile-filtered, and used in contact with the product, primary containers or direct product contact surfaces, shall be periodically monitored for the presence of microorganisms.

14.3.2 Additional microbial characterization

The microbiological environmental monitoring programme shall include periodic characterization of the environmental flora/isolates to allow an assessment of the risk to the product.

14.3.3 Microbiological sampling techniques

Air sampling, using a volumetric sampling method, and other sampling methods, e.g. settle plates, swabs and contact plates, shall be used as appropriate to evaluate the microbiological quality of zones within the APA.

14.4 Particulate environmental monitoring programme

Particulate monitoring programmes shall be implemented for areas or equipment where product quality, personnel safety or testing accuracy can be affected by particulates or environmental conditions.

15 Alert and action levels

15.1 Development of alert and action levels

Alert and action levels shall be developed for all sampling sites in the APA.

NOTE 1 Alert and action levels should be derived from and consistent with results obtained during the aseptic process validation. Historical data from routine monitoring may also be appropriate for use in setting alert and action levels.

NOTE 2 Often one level is appropriate, serving both as alert and action levels for critical processing zones.

NOTE 3 Adjustments of alert and action levels could be appropriate, based upon the results of the periodic media-fill re-evaluations and associated environmental monitoring data.

15.2 Review of data

The results of all environmental monitoring shall be reviewed in a timely manner against the alert and action levels established for the facility, and the impact on the product's quality shall be assessed.

If the environmental monitoring programme indicates that specified limits are exceeded, corrective action should be taken.

15.3 Environmental monitoring trend analysis

15.3.1 Environmental data shall be analyzed for trends on a routine basis.

15.3.2 An investigation shall be initiated when necessary as indicated by trend data.

16 Investigations and reports

16.1 Investigation action plans

16.1.1 Investigations shall be conducted for unusual circumstances, extended mechanical breakdowns, or when action levels are exceeded.

16.1.2 Written investigation procedures shall be available and shall include determination or review of the following:

- a) data to be collected;
- b) extent of the problem;
- c) impact on product or environmental control;

- d) quarantine of the product;
- e) whether environmental control has been attained;
- f) follow-up testing; and
- g) notification of affected responsible personnel.

16.2 Investigation testing

Investigation testing shall be designed to locate the source of the problem and demonstrate that the area, process or equipment is once again under control. Revalidation may be necessary based on the outcome of the investigation.

16.3 Investigation report

16.3.1 The investigation shall be documented in a report.

16.3.2 The report shall be reviewed and approved by management and distributed to all key personnel associated with the aseptic processing operation.

16.3.3 Where appropriate, the report shall also contain future corrective actions and recommendations for disposition of product.

17 Media fills (process simulation tests)

17.1 Operational control

The control of aseptic operations is dependent on and maintained by well-trained personnel, defined procedures and appropriately designed equipment and facilities (see Introduction.) Media filling in conjunction with comprehensive environmental monitoring can be particularly valuable in demonstrating that the aseptic processing of sterile solutions, suspensions, and powders is functioning as intended. The media fill should simulate the aseptic process as far as reasonably practicable.

NOTE A media fill is a point in a time-representation of the capabilities of an aseptic processing system including environment, equipment and personnel. It does not automatically ensure that products made on the same line at other times will have the same level of microbiological quality. However, through control and validation of all related processes, such as environmental monitoring, qualification of personnel, and validation of cleaning and sterilization cycles, it is possible to maintain the level of product quality demonstrated by the media-fill programme.

17.2 Initial performance qualification

17.2.1 Performance qualification shall be conducted for each new aseptic filling line and for each new product/container configuration which has not been represented in a previous performance qualification.

17.2.2 Performance qualification shall consist of media-fill studies of a product/container configuration which is representative of the actual product to be filled. Representative criteria include:

- a) the actual product/container configuration that is representative of other filled products on the filling line;
- b) two products which bracket all others with respect to size, fill, container opening, line speed, manipulations, etc.;

- c) products which have been deemed to be the worst case with respect to the opportunity for contamination, e.g. a container which has the largest opening and is conveyed at the slowest line speed.

17.2.3 Performance qualification acceptance criteria shall meet the requirements of Table 1.

Table 1 — Initial performance qualification — Media-fill acceptance criteria

Production batch size (number of units)	Minimum number of media fills	Minimum number of total filled units	Media-fill ALERT LEVEL and required action	Media-fill ACTION LEVEL
< 500	≥3, as necessary, to achieve total number filled units	5 000 ^{1), 2)}	One (1) contaminated unit in any run; Investigate cause, conduct one (1) additional run; (repeat performance qualification if the additional run fails).	Two (2) contaminated units in a single run, or one (1) each in 2 runs; Cease qualification media fills; investigate cause; repeat initial qualification media fills.
≥500 to 2 999	≥3, as necessary, to achieve total number filled units	5 000 ¹⁾	As above	As above
≥ 3 000 ³⁾	3 fills of at least 3 000 units per run	9 000	As above	As above

1) Since less than 3 000 units would be filled in any one run, Table 3 cannot be directly applied; however, on an empirical accumulative basis, no positive units in each of the individual media-fill runs would be suggestive of a low contamination level.
2) See 17.2.4 regarding considerations for small or infrequent production or clinical batches.
3) The number of units filled in a media-fill run should allow for interventions that are routinely encountered during production. See 17.2.4 and 17.5.4.

The number of runs and total filled units are summarized below. Media fills relative to a), b) and c), below, shall contain a number of units at least equal to the maximum production batch size.

- a) For production batch sizes of less than 500 units, a minimum of three media-fill runs, for a total of 5 000 units, shall be conducted.
- b) For small, infrequently filled production or clinical batches (< 500 containers, filled less than four times per year) that are filled on established, qualified manufacturing equipment in a controlled environment, it shall be acceptable to conduct three media fills preceding the fill.
- c) For production batch sizes between 500 and 2 999 units, a minimum of three media-fill runs, for a total of 5 000 filled units, shall be conducted.
- d) For production batch sizes of 3 000 units and greater, a minimum of three media-fill runs of 3 000 each, for a total of 9 000 filled units, shall be conducted.

NOTE It may be necessary to fill more than 3 000 units per media-fill run in order to accommodate process variables and interventions routinely encountered during production.

17.3 Periodic performance requalification

17.3.1 Scheduled media-fill requalifications shall occur at least every six months for each product/container configuration and aseptic filling line.

17.3.2 Aseptic filling lines and product/container configurations used less frequently than every six months shall be requalified with an acceptable media-fill test.

17.3.3 Product manufacturing may resume while the media-filled units are being incubated; however, product release shall not occur until acceptable media-fill data are obtained.

NOTE Media-fill requalification of the process or line prior to the scheduled six-month interval should be considered in cases of facility and equipment modification, changes in personnel, anomalies in environmental testing results or end product sterility testing.

17.3.4 Requalification acceptance criteria shall meet the requirements of Table 2. The number of runs and total filled units are summarized as follows:

- a) For small production batch sizes (< 500 containers), three media-fill runs of the maximum batch size shall be conducted.
- b) Alternatively, for small, infrequently filled production batches or clinical batches, (< 500 containers filled less than four times per year), it shall be acceptable to requalify the process or line by performing a single media-fill run, containing a quantity of units at least equal to the production batch, immediately after the production batch is filled.

NOTE Any necessary measures should be taken to assure inactivation or elimination of antimicrobial residuals in filling lines prior to conducting a media fill.

- c) For production batch sizes between 500 and 2 999 units, one media-fill run of at least the maximum batch size shall be conducted.
- d) For production batch sizes greater than 3 000 units, one media-fill run of at least 3 000 units shall be conducted.

NOTE It might be necessary to fill more than 3 000 units per media-fill run in order to accommodate process variables and interventions routinely encountered during production.

17.4 Repeat of initial performance qualification

17.4.1 When required, repeat of performance qualification shall be conducted using the same procedures, methods and acceptance criteria as described in 17.1.

17.4.2 An aseptic process or filling line shall be subject to repeat of performance qualification studies when:

- a) an action level is exceeded, unless an assignable cause for the exceeded action level is identified;
- b) production lines have not been in operation for an extended period of time, e.g. one year;
- c) there has been a significant change.

NOTE Documented change control procedures should identify significant changes, such as:

- modifications in equipment directly contacting bulk product or product/containers
- modifications in equipment or facilities which can affect air quality or flow
- major changes in production personnel, e.g. new crews
- initiation of additional production shifts

17.5 Media-fill procedures

17.5.1 Media fills shall be conducted on separate days, at different times during the normal working period.

17.5.2 A list of permitted and proscribed intervention events that could occur during the aseptic processing shall be available.

17.5.3 Media fills shall be conducted under processing conditions that include "worst-case" conditions, e.g. the greatest practical number of permitted interventions, correction of line stoppage, repair or replacement of filling needles/tubes, replacement of on-line filters, number of personnel involved, etc. The duration of media fills may need to be adjusted for special processes where planned interrupted filling occurs.

17.5.4 The media-fill run shall be of sufficient duration to cover most manipulations and operations that are normally performed in actual processing.

NOTE If multiple sizes of the same container/closure configuration are aseptically filled, selective sizes may be used for media fills. Containers with the widest diameter openings and lowest line speed should be included in the media-filling regimen and might be representative of worst-case conditions. However, there are cases where small containers are representative of worst-case conditions because of lack of container stability in the line operations and the need for increased manual intervention.

Table 2 — Periodic requalification — Media-fill acceptance criteria

Production batch size (number of units)	Number of media fills	Minimum number of units per media fill	Media-fill ALERT LEVEL	Media-fill ACTION LEVEL
< 500	$\geq 3^{(2)}$	Maximum batch size ¹⁾	One (1) contaminated unit in any run; cease requalification; investigate cause; repeat periodic requalification.	Two (2) contaminated units in a single run; cease requalification; investigate cause; repeat initial qualification per Table 1
≥ 500 to 2 999	1	Maximum batch size ¹⁾	As above Repeat the media-fill run.	As above
$\geq 3\ 000$ ³⁾	1	3 000	Repeat the media-fill run if the alert values in Table 3 are exceeded.	See Table 3 for maximum action level values.

1) Since less than 3 000 units would be filled in any one run, the 95 % confidence limit table cannot be directly applied; however, on an empirical accumulative basis, no positive units in each of the individual media-fill runs would be suggestive of a low contamination level. Reference Table 3.
2) See 17.2.4 regarding considerations for small or infrequent production or clinical batches.
3) The number of units filled in a media-fill run should allow for interventions that are routinely encountered during production. See 17.2.4 and 17.5.4.

17.6 Media selection and growth support

17.6.1 Verification of growth promotion of media used in specific media-fill runs shall be conducted following the run.

17.6.2 The incubation temperature shall be the same as that used for the media-filled units.

17.6.3 The media selected for media-fill runs shall be capable of growing a wide spectrum of microorganisms and of supporting microbiological recovery and growth of low numbers of microorganisms, i.e. 100 colony-forming units (CFU)/unit or less.

NOTE Growth-promotion test units should demonstrate growth of the test organisms in conformance with pharmacopoeial requirements. Such tests should be conducted within the actual media-filled containers where possible.

17.7 Incubation and inspection of media-filled units

17.7.1 Leaking or damaged media-fill evaluation units shall be removed, and a record made of such removal, following processing and prior to incubation of the media.

17.7.2 Media-filled evaluation units shall be incubated for a minimum of 14 days.

17.7.3 Incubation temperatures shall be appropriate for the specific growth requirements of microorganisms that are anticipated in the aseptic filling area.

NOTE Environmental monitoring data can assist in identifying the optimum incubation temperatures. Frequently-used temperatures ranges for incubation are 20 °C to 25 °C and 30 °C to 35 °C, or 28 °C to 32 °C.

17.7.4 Media-filled units shall be stored or manipulated to allow contact of the media with all product contact surfaces in the unit.

17.7.5 After completion of the incubation period, the media-filled containers shall be visually inspected for the presence of microbial growth.

17.7.6 Microorganisms present in contaminated units shall be identified to help determine the likely source of the contamination.

NOTE 1 Inspection of the units at an earlier time period (3 d to 7 d incubation) can be useful to gain a preliminary indication of the results.

NOTE 2 Media-filled units should be chronologically identified within the batch to help identify the time at which a contaminated unit was filled.

17.8 Acceptance criteria

17.8.1 General

A contamination rate of 0,1 %, with a 95 % confidence level, shall not be exceeded in a media fill of not less than 3 000 units.

NOTE 1 This part of ISO 13408 includes a statistical approach for assessing the probable rate of contamination within media fills. The probable rate of contamination is based on the numbers of units filled, and the upper 95 % confidence limit of positives derived from the actual positive units that occurred in the media-fill runs.

NOTE 2 Although this part of ISO 13408 describes a contamination rate of 0,1 % in media fills, manufacturers should strive to achieve a lower rate. Automated rapid-fill lines and filling lines contained within isolators should allow a contamination rate less than 0,1 % for media fills. This is difficult to demonstrate, however, since, for example, 30 000 units would have to be media-filled to demonstrate a contamination rate of 0,01 %.

NOTE 3 See 17.2.3 and 17.3.4 regarding batches of less than 500 units.

Regardless of the values that appear in Table 3, any contaminated units shall be investigated concerning the reason and possible origin of the recovered microorganism(s). It may be necessary to consider the media fill a failure regardless of the number of recovered microorganisms, if the manufacturing environment or product is deemed at risk.

17.8.2 Acceptance criteria tables

17.8.2.1 Table 1 shows the acceptance criteria for initial performance qualification of an aseptic processing line.

17.8.2.2 Table 2 shows the acceptance criteria for requalification of an aseptic processing line.

17.8.2.3 Table 3 shows alert and action levels when a 0,1 % contamination rate is attained for large numbers of media-filled units, i.e when one elects to media-fill greater than 3 000 units.

The action levels in Table 3 are based on a 0,1 % contamination rate. This value was attained by dividing the number of media-filled units by the upper 95 % confidence limit for the presence of positives as calculated by the Poisson distribution formula.

Annex A includes descriptive and derivation information concerning establishment of an upper 95 % confidence level (CL) and the setting of a 0,10 % action level. Examples for calculating the frequency of contamination for a given number of media-filled units are included in annex A.

NOTE 1 Table A.2 presents information showing numbers of contaminated units by size of media fill. Table A.2 serves as supporting data for Table 3.

NOTE 2 Table 3 and Table A.2 are not presented to encourage individual firms to media-fill additional units to permit a greater number of acceptable positives. The tables are presented to demonstrate when at least a 0,1 % contamination rate has not been attained.

Regardless of the number of positives recovered from a media fill, it is incumbent upon the manufacturer to investigate the origin of microbial contamination to ensure that both the aseptic manufacturing environment and product are not at risk.

17.9 Contamination with media

Contamination of the facility and equipment with media during media-fill runs shall not compromise the quality of the facility and equipment or the product subsequently processed using the same facility and equipment. Media shall be handled properly and promptly followed by cleaning, disinfection and, where necessary, sterilization of the equipment.

NOTE The validation of cleaning, disinfection and sterilization methods should demonstrate the removal of media spillage that may have occurred during media-fill runs.

17.10 Data required for media fills

All media-fill runs shall be fully documented, and the following information (where applicable) included with, or cross referenced to, the records for each media-fill run:

Table 3 — Alert levels and action levels for large numbers of media-filled units

Number of units in single media-fill test	Alert level ¹⁾ (number of contaminated units in a single media-fill run)	Action level ²⁾ (number of contaminated units in a single media-fill run)
3 000	Not applicable	1
4 750	1	2
6 300	1	3
7 760	1	4
9 160	1	5
10 520	2	6
11 850	2	7
13 150	3	8
14 440	3	9
15 710	4	10
16 970	4	11

NOTE 1 Any recovered microorganisms shall be investigated related to the reason and possible origin of the recovered microorganism(s) (see 17.8.1).

NOTE 2 A sufficient number of units should be media-filled to permit most interventions and worst-case conditions that may occur during production conditions (see 17.5.4).

1) This alert level is based on selection of a 0,05 % contamination rate.
2) $\geq 0,1$ % contamination rate at a 95 % confidence level.

- a) date and time of media fill;
- b) identification of filling room used;
- c) container/closure type and size;
- d) volume filled per container;
- e) filling speed;
- f) filter lot and catalogue number;
- g) type of media filled;
- h) number of units filled;
- i) number of units rejected at inspection and reason;
- j) number of units incubated;
- k) number of units positive;
- l) incubation time and temperature for each group of units incubated and whether any group of units is subjected to two different temperatures during the incubation;
- m) procedures used to simulate any steps of a normal production fill, which might include, for example, mock freeze-drying or substitution of vial headspace gas;
- n) microbiological monitoring data obtained during the media-fill set-up and run;

- o) list of personnel who participated in the media fill;
- p) growth promotion results of the media removed from filled containers;
- q) identification of the microorganisms from any positive units, and investigation of any contamination events observed during media fills;
- r) management review;
- s) length of time media was stored in holding tank prior to filtration;
- t) length of time taken to fill all containers.

17.11 Media-fill runs exceeding action levels

17.11.1 Investigation

17.11.1.1 When media-fill action levels are exceeded, an investigation shall be conducted and documented regarding the cause.

17.11.1.2 If action levels are exceeded, there shall be a prompt review of all appropriate records relating to aseptic production between the current media fill and the last successful one.

The investigation should include, but not be limited to, consideration of the following:

- a) microbial environmental monitoring data;
- b) particulate monitoring data;
- c) personnel monitoring data (finger impressions, etc.);
- d) sterilization cycles for media, commodities and equipment;
- e) HEPA filter evaluation (airborne particulate levels, smoke-challenge testing, velocity measurements, etc.);
- f) room air flow patterns and pressures;
- g) operator technique and training;
- h) unusual events that occurred during the media fill;
- i) storage conditions of sterile commodities;
- j) identification of contaminants as a clue to the source of the contamination;
- k) housekeeping procedures and training;
- l) calibration of sterilization equipment;
- m) pre- and post-filter integrity test data, and/or filter housing assembly;
- n) product and/or process defects, and/or limitation of inspectional processes; and
- o) documented disqualification of samples for obvious reasons prior to final reading.

17.11.2 Corrective actions

17.11.2.1 Media-fill tests which exceed action levels shall require action as described in Tables 1 or 2.

17.11.2.2 Decisions on whether or not to take action against product being held and/or distributed shall be based upon an evaluation of all the information available and shall be documented.

17.11.2.3 All product that has been produced on a line following the media fill shall be quarantined until a successful resolution of the media fill has occurred.

NOTE A review of production batches in association with an unsuccessful media fill should include appropriate environmental monitoring data, the record of sterility test results over this period of time, possible assignable causes for the current media-fill results, and any other information that would bear upon the sterility of the product involved.

18 Finished-product sterility testing

18.1 General

Sterility testing of aseptically filled products shall be conducted for each batch or lot.

18.2 Investigation of sterility-test positives

18.2.1 Positive sterility-test results shall be evaluated and an investigation shall be initiated to determine the source of contamination, including whether the growth occurred due to contamination during the test.

18.2.2 A correlation assessment between types of microorganisms found in the manufacturing environment, sterility testing room, and isolated from failed sterility tests shall be conducted.

18.3 Sampling plans

18.3.1 Sampling plans for in-process or finished product evaluation shall be developed to assure representation of the entire batch and shall be based on a statistical rationale or other acceptable compendial or regulatory requirements.

18.3.2 The sampling plan shall be representative of the lot.

Samples obtained are considered representative of the lot if:

- a) they are obtained periodically (including beginning, middle and end) throughout the filling run; and
- b) they include units collected after operator intervention in the processing zone(s).

19 Steam-in-place

19.1 General

19.1.1 Equipment which cannot be sterilized in an autoclave due to size or configuration shall be steam-sterilized *in situ* with a demonstrated process lethality of six logarithms reduction, using a moist-heat-resistant biological indicator system for initial qualification and requalification.

The use of heat-resistant microorganisms in validation processes requires appropriate control to minimize potential contamination of the APA.

Steam-in-place allows the entire health care product processing system to be steam sterilized as a single entity, eliminating or reducing the need for aseptic connections. Examples include tanks, filling lines, transfer lines, filtration systems and water for injection systems.

A steam-in-place process requires the precise execution of procedures for the removal of air and condensate, as well as for the integrity of the system once the process has been completed. Minor deviations from the established procedure can result in process failure, which could remain undetected. The following measures should be addressed for steam-in-place systems:

- a) displacement and elimination of entrapped air by gravity or vacuum methods;
- b) constant bleeds or steam traps at all low points to eliminate condensate build-up;
- c) strict adherence to the steam-in-place procedures;
- d) proper maintenance of the integrity of the system after the process;
- e) strict adherence to the maximum filter specifications for temperature, pressure and flow; and
- f) avoidance of back-pressure on filters during steam-in-place.

19.1.2 In the absence of an automated SIP system, manual procedures shall be defined, adhered to, and documented.

19.2 Post-sterilization system integrity

19.2.1 System integrity shall be maintained after sterilization.

19.2.2 Gases (air or nitrogen) introduced into the total system shall be sterile.

19.2.3 The system shall then be purged of steam and condensate and maintained under positive pressure until ready for use.

NOTE The introduction of a sterile gas (e.g. air or nitrogen) can dry the system prior to use, which is very important if the product to be processed is non-aqueous.

20 Process filtration

20.1 Filter and filter equipment evaluation programme

20.1.1 A documented filter evaluation programme shall be established prior to validation and acceptance of filters.

This programme should include evaluation of the following:

- a) pertinent manufacturer data regarding filters and filter components (membranes, cartridges, support structures, end-caps, gaskets, O-ring material, etc.);
- b) procedures for integrity testing;
- c) filter and product compatibility;
- d) filter extractables and particle shedding.

The shedding or media-migration characteristics of the filter should be evaluated based on the intended life of the filter.

20.1.2 Product-sterilizing filters shall be evaluated by an appropriate and defined bacterial challenge test, or evidence of product-specific data from the filter manufacturer shall be available.

NOTE Microbiological evaluation tests should be conducted during the initial qualification stages within a laboratory environment as conducting such tests in a manufacturing environment could jeopardize the quality of the environment.

20.1.3 Absorption or adsorption from the product by the filter shall be evaluated.