INTERNATIONAL STANDARD

ISO 13408-1

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Aseptic processing of health care products —

Part 1:
General requirements

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

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Foreword

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

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: Filtration*[1)]

— *Part 3: Freeze-drying*

— *Part 4: Sterilization and cleaning in place*[1)]

— *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.

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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) hange 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.