6.6 Cleanroom qualification

The cleanrooms shall be qualified to demonstrate that they meet the requirements as specified in the ISO 14644 series and applicable regulatory guidelines respectively and that they are compatible with the manufacturing environmental contamination control programme at rest and under operational conditions. This shall be demonstrated in a formal qualification programme.

6.7 Utility services and ancillary equipment

6.7.1 General

6.7.1.1 Utility services provided for the APA shall be designed, located and installed such that the cleanroom is not compromised by contamination from such services.

6.7.1.2 Manufacturing, storage and distribution systems for process related utilities such as purified water, water for injection(s), compressed air (and/or other gases), clean steam, and cleaning-in-place/sterilization-in-place shall be validated.

6.7.2 Water and wastewater

6.7.2.1 No water taps, basins or sinks shall be provided in ISO 14644-1:1999, Class 7 or better areas. Where water is needed for functioning of equipment (e. g. cooling water) this shall be contained in a closed system so that contamination of the APA is prevented. The integrity of the closed water cooling system shall be confirmed at a defined frequency.

6.7.2.2 Water used in the process in ancillary areas (e.g. for washing of primary packaging material) shall be of suitable quality to prevent contamination being introduced to the process. The water used in the process shall comply with the requirements in Annex C.

6.7.3 Gases

All compressed gases (excluding combustible gases) that enter the aseptic facility shall be dry and oil-free and those that come into contact with sterile products, container/closures or critical surfaces shall be filter sterilized and periodically monitored for the presence of microorganisms and particulates. Integrity of the sterilizing filters shall be assured before use of the filter and at regular defined intervals, preferably by in-line testing.

6.7.4 Vacuum utilities

6.7.4.1 If portable vacuum cleaning equipment is used it shall be fitted and tested with an exhaust filter of at least the same efficacy as that filtering the air used for venting the area.

6.7.4.2 If a fixed vacuum source is used it shall be designed to prevent backflow.

6.8 Environmental and personnel monitoring programmes ((6.8 as revised by the Convenor))

6.8.1 General

6.8.1.1 The APA shall be monitored for viable and particulate contamination following a defined, documented programme that describes the routine particulate and microbiological monitoring of processing and manufacturing areas, and includes a corrective action plan when specified action levels are exceeded.

NOTE See Annex D including information on different zones and areas.

6.8.1.2 Specifications shall be set in compliance with appropriate particulate control standards following ISO 14644-1:1999, ISO 14698-1 and ISO 14698-2 and/or relevant GMP requirements and taking into account

the risk estimation conducted as part of the aseptic processing concept, and the results of validation studies performed.

6.8.1.3 The defined documented sampling plan shall describe at least:

a) sites monitored;

b) frequency of monitoring;

c) conditions for monitoring (static and/or dynamic);

d) method of monitoring including procedure, duration of sampling and sample size;

e) alert level and action levels;

actions taken when alert and action levels are reached.

6.8.1.4 For new facilities, the frequency of monitoring for the different zones shall be specified, preferably based on cleanroom qualification data and in consideration of facility/equipment design, processing parameters and the type of product and process.

6.8.1.5 The frequency of routine monitoring for the different zones shall be specified, based on historical environmental monitoring data and with due consideration of the minimal requirements as given in relevant guidelines.

6.8.1.6 The critical processing zone shall be monitored during each operational shift.

6.8.1.7 Direct and indirect support zones shall be monitored less frequently than the APA at a defined frequency which allows to recognize trends in the data collected. Frequencies shall be established in consideration of the manufacturing environment, the contamination control programme and historical testing data.

6.8.1.8 Due to the limitations of fixed site sampling plans, the routine sampling plan shall include a provision for periodic surveillance monitoring at additional sites during and/or after operations. The sites selected should be related to activities which present possible contamination risks to the product.

NOTE An example of such additional sampling sites is the surface of tools used for interventions in the critical processing zone.

6.8.1.9 Additional monitoring shall be performed following initial start-up of operations or following periods of extended shutdown or modifications to the facility.

6.8.2 Sampling for particulate monitoring

The particulate monitoring programme for areas or equipment in the aseptic processing facility where product quality or testing accuracy can be affected by particulates shall be in compliance with ISO 14644-2.

NOTE 1 It is accepted that it may not always be possible to demonstrate conformity with particulate standards at the point of product exposure when aseptic processing is going on due to the generation of particles or droplets from the process itself.

NOTE 2 In certain jurisdictions continuous or frequent sampling of particles is required for the critical processing zone and is recommended for the direct support zone.

6.8.3 Sampling for microbiological environmental monitoring

6.8.3.1 The sampling plan for microbiological monitoring shall contain in addition to 6.8.1.3 the designation of sites monitored by active and passive air monitoring, and sites for surface monitoring, including equipment surfaces.

6.8.3.2 Sampling sites shall be located where components and product are exposed to the environment. Sites shall be derived from and be consistent with those used during validation activities and represent the highest microbiological risk to the product. Rationale for sites chosen shall be documented.

6.8.3.3 Air samples shall be collected at the time of normal activity. Product contact surfaces shall be only monitored after completion of the filling operation to prevent the risk of contamination of the product.

6.8.4 Monitoring of personnel

6.8.4.1 Personnel trained and qualified to work in the APA shall be subject to a routine microbiological monitoring programme. Monitoring data shall be used to identify trends and evaluate the need for retraining.

Personnel present in the direct support zone and/or critical processing zone shall give finger prints daily. At defined intervals samples from the gowns shall also be taken (e.g. both forearms, chest, hood). After a garment has been tested for microbial contamination it shall not be worn in the APA until cleaned and sterilized.

NOTE The frequency of sampling gowns and gloves is based on the nature of the activities performed.

6.8.4.2 Personnel found to consistently exceed established microbiological levels shall be investigated and removed from work in classified zones. Procedures shall be established for retraining and requalification. Satisfactory performance shall be demonstrated prior to the personnel concerned being reassigned for work in classified zones.

6.8.5 Monitoring procedures

6.8.5.1 The APA shall be routinely monitored for the presence of microorganisms on each shift by use of quantitative air sampling using volumetric sampling methods, and semi-quantitative sampling methods, e.g., settle plates, swabs, and contact plates as appropriate. For active sampling calibrated equipment shall be used. A rationale for the sampling methodology shall be documented.

6.8.5.2 Growth media used shall be shown to allow recovery of yeast, moulds and other microorganisms which may occur in the manufacturing environment and/or product. The justification for the media selected and the microorganisms used to establish their growth promoting capacity shall be documented.

6.8.5.3 Sampling in the critical processing zone shall be performed in a manner which presents no contamination risk to the product.

6.8.5.4 The microbiological environmental monitoring programme shall include characterization of the recovered microorganisms (isolates) to facilitate a continued assessment of the risk to the product.

NOTE All isolates from the critical processing zone are speciated where feasible. The depth of routine characterization or identification of isolates from other zones will depend on the location of the sampling site within the APA.

Differentiation of microbiological isolates shall be part of failure investigation in case of exceeded action levels.

6.8.6 Evaluation of monitoring data

6.8.6.1 Alert and action levels

Alert and action levels shall be developed for all sampling sites in the APA. For the critical processing zone, each microorganism detected should be investigated. Alert levels and action levels shall be reviewed at defined, regular intervals. Alert levels in the APA should be derived from and be consistent with results obtained from data trend analysis.

For the critical processing zone one level is appropriate serving both as alert and action levels. Each microorganism detected shall be investigated.

NOTE 1 Action levels in support zones are typically based on regulatory guidance.

A result at the alert level urges attention to the approaching action conditions.

NOTE 2 For new facilities consideration of microbiological monitoring data from historical databases, process simulations, cleanroom qualification, and sanitization studies are frequently used in developing monitoring levels.

6.8.6.2 Review of data and trend analysis

6.8.6.2.1 The results of each individual sample result of environmental monitoring within the critical processing zone during the period of manufacture shall be reviewed against the alert and action levels established for the APA prior to batch release. The impact of any excursions on the product's quality shall be assessed.

NOTE Averaging of results without due consideration of individual high values can mask unacceptable localized conditions.

6.8.6.2.2 Environmental data (both counts and the type of microbial flora) shall be analysed for trends on a routine basis. A trending report giving an overview over all environmental observations and trends shall be issued in fixed intervals. Trend reports should include data generated by location, shift, room, operator or other parameters. An investigation shall be initiated when necessary as indicated by individual excursions and/or trend data.

NOTE 1 It is important not to ignore correlations between sampling sites as single site trends may not provide a complete representation of the environment being monitored.

NOTE 2 Examples of trends leading to an investigation include:

a) a trend towards higher numbers of microorganisms at a sampling site;

b) repeated occurrence of microorganisms not previously encountered.

6.8.6.3 Investigations and reports

6.8.6.3.1 Investigations following documented procedures shall be initiated following events that indicate a possible loss of environmental control such as:

a) excursion above action levels

b) excursions above alert and/or action levels indicating a possible adverse trend,

c) an increased incidence of microbial growth below the action level and above historical levels,

d) unusual circumstances are encountered or persist (e.g. extended mechanical breakdowns).

e) audit observations indicating a possible increase in contamination risk or

f) a documented adverse trend

NOTE 1 Elements for consideration in course of the investigation include, e. g.:

a) extent of the problem,

b) data to be collected (e. g. surveiilance monitoring at additional positions),

c) extent of review of environmental control data,

d) potential impact on product (e.g. need for quarantine of product),

e) follow-up testing, and

f) notification of affected responsible personnel.

NOTE 2 Additional testing can be required for, e. g.:

a) identification of source(s) of the contamination;

b) determination of possible impact of a deviation on product quality;

c) demonstration that any corrective actions were successful and the area is once again under control

6.8.3.3.2 The investigation shall be documented in a report. The report shall be reviewed and approved by qualified personnel and distributed to the responsible key personnel.

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

7 Equipment

7.1 Qualification

7.1.1 General

Equipment used in the aseptic processing or associated testing, such as component washers, sterilizers, filter assemblies, sterilization filters, closure placement equipment, sealing machinery and lyophilizers shall be qualified to assure their suitability for the intended purpose .

NOTE This International Standard deals only with features specific to aseptic processing. Equipment qualification is a wider concept and additional considerations are needed for technical qualification.

7.1.2 User requirements

A user requirements document shall be generated defining the equipment functionality and performance required. It shall be reviewed and approved by the user. Considerations (in addition to other technical or safety questions) shall include, where appropriate, e. g.:

a) surface finish quality;

b) specification for capability of being cleaned;

c) specification for capability of being sterilized;

d) ease of access for aseptic assembly;

e) avoidance of recesses in or underneath the equipment;

f) suitable arrangement of utility piping, tubing, or cables for aseptic operation;

g) ease of access of internal workings without putting the APA at risk including ability to service the equipment from outside, wherever possible;

h) ease of mechanical and electrical adjustments from outside the critical processing zone wherever possible or ease of access with minimal disturbance of the critical processing zone;

i) compatibility of equipment handling with operation in an isolator, where applicable;

j) sealing of computers and keyboards;

k) fitting of equipment with an exhaust with filters so that the exhaust is of at least the same air quality grade as that of the area into which it is discharged;

l) if the equipment is to be cleaned-in-place or sterilized-in-place.

7.1.3 Design qualification

7.1.3.1 Equipment shall be designed for use in the specified clean zone and shall meet the functional and safety requirements relevant for its intended.

7.1.3.2 Documented evidence shall be collected to demonstrate suitability of the equipment for the intended product or process.

7.1.4 Installation qualification

7.1.4.1 Installation qualification shall be carried out in accordance with a documented procedure which shall cross-reference appropriate equipment and "as installed" specifications. Documented evidence shall be collected to verify that the equipment is supplied and installed suitably for operation in the APA. Instruments shall also be calibrated before operational qualification.

7.1.4.2 Operating instructions shall be available.

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

7.1.5 Operational qualification

Documented evidence shall be collected to demonstrate that the equipment can be operated in the APA so that specified cleanroom conditions are maintained. For equipment operated in the critical processing zone, ISO 14644-1:1999, Class 5 conditions or better shall be maintained under all routinely encountered operating conditions. Operational qualification shall demonstrate that the installed equipment is capable of performing the specified process within the defined operating range.

NOTE Specific items that are typically addressed during operational qualification for equipment used in aseptic processing include, e. g.:

a) integrity of barriers;

b) verification of air flow pattern and air quality;

c) verification of alarm systems.

7.1.6 Performance qualification

7.1.6.1 Requirements shall be established for performance qualification. Performance qualification shall include a demonstration that the equipment is consistently operating to yield sterile product.

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

7.1.6.3 Data shall be generated to demonstrate the attainment of defined physical and/or chemical conditions within specified tolerances throughout the process

7.1.6.4 Documented evidence shall be collected to demonstrate that the equipment will maintain consistent segregation and operate with minimal interventions when operated under worst case challenge conditions which could jeopardize product protection.

7.1.7 Requalification

7.1.7.1 An evaluation of the need to perform requalification of processes carried out with specified equipment shall be performed at defined intervals and in response to aseptic process events.

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

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

7.2 Maintenance of equipment

7.2.1 Scheduled preventive maintenance

7.2.1.1 Utilities, services and equipment shall be part of the preventive maintenance programme.

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

7.2.1.3 Tools and other maintenance aids shall be:

a) of suitable design;

b) capable of being cleaned;

c) capable of being disinfected or sterilized;

d) appropriately stored to prevent contamination.

7.2.1.4 Maintenance procedures shall be established and documented with due consideration of APA requirements.

7.2.1.5 Where integrity of the APA cannot be maintained during maintenance, the area shall be taken out of service and not be reused before it has been subjected to a defined cleaning procedure or before the area has been requalified.

7.2.2 Unplanned maintenance

7.2.2.1 During aseptic operation unplanned maintenance shall be performed using aseptic techniques and only to the extent that has been simulated during process simulation. If the unplanned maintenance has not been qualified the process shall be stopped and any exposed units of product be removed from the process and disposed of appropriately.

7.2.2.2 Restart of the process after unplanned maintenance shall follow established procedures assuring that the specified process conditions have been re-established.

Where integrity of the APA cannot be maintained during maintenance the area shall be taken out of service and not be reused before it has been subjected to a defined cleaning procedure or before the area has been requalified.

8 Personnel

8.1 General

8.1.1 Documented procedures for personnel training and assessment of personnel performance shall be established and implemented. Management shall be responsible for defining criteria to assess personnel performance. These criteria shall include, at a minimum, process simulation participation, gowning qualification and compliance with procedures.

8.1.2 Defined procedures shall be in place to assure that personnel do not compromise aseptic processing environmental conditions. The effectiveness of the documented procedures shall be evaluated at intervals defined by the manufacturer.

8.1.3 Management shall be responsible for implementing an appropriate training programme to ensure that personnel (including supervisors, QA staff and maintenance staff) are appropriately qualified before entering or being assigned work in the APA, as defined in 8.2.

8.2 Training for APA qualification

8.2.1 All personnel entering the APA including those who require only temporary access shall be qualified based on successful completion of defined training. Training in the various disciplines and activities should be in proportion to the individual's duties and directed at the appropriate level of knowledge.

8.2.2 All personnel working in the APA shall be trained with reference to e. g.:

a) design and necessary functionality of the facility contamination control concept including awareness of segregation, barriers, monitors and alarms;

b) microbiological risk assessment and risk prevention;

c) fundamentals of microbiology;

d) personal hygiene, e.g. hand washing and disinfection procedures;

e) rules concerning the wearing of cosmetics, wristwatches or jewellery;

f) manufacture of sterile products within the APA;

g) aseptic technique;

h) gowning procedures;

i) cleanroom practices;

j) emergency procedures to protect product quality, e. g., failure of HVAC system, loss of power, etc.

8.2.3 Training in cleanroom practices shall include an overview of operator impact on the APA and the manufacturing process. Specifically this training ensures operators are knowledgeable in good aseptic technique and practices to avoid, e.g.:

a) any contact with critical surfaces including sterilized materials and components,

b) unnecessary contact with walls, floors and cleaned surfaces,

c) unnecessary and/or rapid movements which can generate particles or create turbulence,

d) unnecessary talking,

e) reaching across open containers and exposed product and components, and

f) blocking air flow over critical surfaces.

8.2.4 Gowning qualification shall include observation of technique and microbiological monitoring. This monitoring shall include multiple locations on the gown. Verification of results shall be documented and communicated to the personnel and management.

8.2.5 Gowning qualification shall be repeated at a frequency defined by the manufacturer (at least annually), based on the nature of the operations performed.

8.2.6 Non-APA personnel (including visitors), who require temporary access to the critical processing zone and direct support zone while in operation shall have been qualified. To enter other zones they shall be accompanied at all times by a person who has been qualified.

Access of visitors to the APA should be minimized. It is preferable to have visitors remain outside the critical processing zone and direct support zone .

98.2.7 All personnel that directly participate in setting up aseptic manufacturing equipment, filling or manufacture of sterile products or maintenance work in the critical processing zones shall take part in a process simulation that meets the requirements of this International Standard at least once per year.

8.2.8 New personnel who will work in the critical processing zone shall take part in at least one process simulation or equivalent aseptic operations, which may be performed in a training environment, before being permitted to participate in processes carried out in critical processing zones.

8.2.9 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.

8.2.10 Training shall be documented and its effectiveness shall be assessed as appropriate (e. g. by oral or written tests, successful participation in practical exercises or in process simulation). Records of training and evaluation shall be maintained.

8.3 Gowning procedures

8.3.1 General

8.3.1.1 Gowning requirements shall be established consistent with the aseptic processing steps, facility contamination control assessment and the segregation requirements for the APA.

8.3.1.2 The gowning cascade shall include

a) removal of street wear

b) putting on factory uniform

c) putting on indirect support zone clothing

d) putting on critical processing zone and direct support zone clothing

NOTE It is possible to go from b) to d) using a dedicated changing room.

Personnel shall not wear direct or indirect support clothing outside the classified areas.

8.3.1.3 The maximum number of people which can be in the gowning air lock simultaneously shall be defined.

8.3.2 Gowning for entering the APA

8.3.2.1 Documented procedures shall be implemented to assure that personnel do not compromise the aseptic processing environment. The procedures shall address:

a) removal of outside garments, wristwatches, jewellery, cosmetics and shoes;

b) hand washing and/or hand disinfection

c) specification of the complete set of cleanroom garments;

d) stepping over barriers in compliance with the segregation concept;

e) sequence of putting on the cleanroom garments;

f) techniques of gowning and de-gowning;

g) washing and validated sterilization procedures for gowns.

The permissible number of washing cycles for the gowns shall be defined.

8.3.2.2 Hair and where relevant beard and moustache should be covered. A single or twopiece trouser suit, gathered at the wrists and with high neck and appropriate shoes or overshoes should be worn. They should shed virtually no fibres or particulate matter.

8.3.2.3 Sterilized garments for critical processing zone and direct support zone shall fully cover the body. There shall be no exposed areas of the face. The garments shall retain particles while allowing passage of moisture vapour for wearing comfort. The fabric shall minimize particle shedding.

Fresh garments shall be used each time a person enters these zones.

NOTE 1 Sterile garments for critical processing zone and direct support zone are frequently composed of a one-piece suit, hood, overboots, gloves, face-mask and goggles.

NOTE 2 Some clean room operations use arm covers, extra high boots and double gloves to minimize the likelihood of gaps or tears occurring during movement.

NOTE 3 Typically clean room gowns are washed in a dedicated facility, individually packed in sterilizable bags and sterilized by steam or irradiation.

Garments worn in the APA shall fit the individual operator.

NOTE 4 For example, a large gown on a small individual could create a bellow-like effect and, in the process of normal operations, the gown bellows outwardly emitting microorganisms and particulates into the room. Conversely, a small gown may not provide adequate coverage of hair and skin.

8.3.2.4 Employees shall wear gloves in critical processing and direct support zones.

NOTE Two pairs of gloves are frequently used; the first pair of gloves may be used as gowning gloves.

8.3.2.5 Before entering the clean zones the correct fit and integrity of the gowns and gloves shall be verified at least in a mirror.

Care should be taken to ensure that at the areas where clothing meet (such as the lower leg, wrist and neck) no gaps or exposed skin are apparent.

8.3.2.6 Personnel in ISO 14644-1:1999, ISO Class 8 or lower areas shall wear garments designed to minimize particulate generation but these garments normally need not be sterile prior to use.

8.4 General employee health

8.4.1 Personnel working in the APA shall be required to report conditions which may affect aseptic work such as fever, skin lesions, common cold, diarrhoea, etc.

8.4.2 Personnel with reported or observed health conditions affecting aseptic work shall not be permitted to enter the APA but may be assigned work in other areas.

9 Manufacture of the product

9.1 Attainment and maintenance of sterility

9.1.1 Component sterilization

9.1.1.1 Raw materials, intermediates and components introduced into the critical processing zone shall have been sterilized with an expiry date defined.

9.1.1.2 Each of these sterilization processes shall be independently validated in accordance with ISO 11135-1, series ISO 11137 and ISO 17665-1.

9.1.1.3 Suitable protection after sterilization shall be provided to prevent recontamination by continuous handling (e. g. conveying) in the critical processing zone or by suitable wrapping, storage and transfer procedures.

9.1.2 Depyrogenation

9.1.2.1 Materials used to manufacture parenteral and other products required or claimed to be free from endotoxins shall comply with a limit test for endotoxins defined and justified by the manufacturer. This applies to raw materials (including water), intermediate products (such as bulk solutions or suspensions) and other components (such as container components) used as part of the product. The levels of endotoxin shall be determined by pharmacopoeial procedures (such as those described in the EP, JP and USP) unless it is necessary, taking into account the nature of the product, for the manufacturer to define and document an alternative or modified test procedure.

9.1.2.2 Data shall be available to demonstrate a knowledge of the endotoxin burden on components prior to treatment in a depyrogenation process.

9.1.2.3 When a depyrogenation process is used validation studies shall be performed to demonstrate that the process will remove a greater quantity of endotoxin than might have been originally present in the component or product.

NOTE 1 Typically reduction of at least 3 orders of magnitude of spiked endotoxin is required to be removed in dry heat sterilizers or rinsing procedures.

NOTE 2 Plastic medical devices, closures and/or containers can be depyrogenated by rinse processes, and/or high temperature moulding and/or extrusion processes prior to filling. Rubber compound stoppers can be rendered pyrogen-free by multiple cycles of washing and rinsing prior to final steam sterilization.

9.1.3 Product sterilization

9.1.3.1 Where the product is manufactured using aseptic technique the materials used in its manufacture (including raw materials incorporated directly in the product, bulk suspensions prepared in advance, and container components) shall be sterilized where possible using validated methods of sterilization appropriate to the specific material (such as moist heat sterilization, radiation sterilization or ethylene oxide sterilization). The method of sterilization shall be justified. The requirements of relevant ISO standards, ISO 17665-1, series ISO 11137, and ISO 11135-1 as appropriate shall be complied with.

9.1.3.2 Where the product is manufactured using sterilization based on sterile filtration then the requirements of ISO 13408-2 shall apply. In addition, container components shall have been sterilized prior to use using a suitable validated method selected taking into account the nature of the material being sterilized. The choice of sterilizing method shall be justified.

91.1.3.3 Where it is not possible to sterilize some materials e. g. live tissues or live vaccines the procedures to achieve products of the required quality shall be specified.

9.2 Duration of the manufacturing process

The total time for each unit operation of an aseptic process shall be minimized and limited to a defined maximum. Examples include:

a) holding time for formulated bulk prior to filtration, where applicable

b) holding time for sterilized components prior to filling/assembly;

c) filling or aseptic assembly;

d) holding sterile product prior to filling;

e) component washing and sterilization.

9.3 Aseptic manufacturing procedures

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

9.3.2 Aseptic manufacturing procedures shall be described in detail in documented operating procedures. The procedures shall specify the sequence of steps to be performed, their execution, their time course and any permitted interventions.

9.4 Cleaning and disinfection of facilities

9.4.1 General

9.4.1.1 A cleaning and disinfection programme for the APA shall be established.

9.4.1.2 Justified procedures shall be in place to evaluate, approve and control the use of cleaning agents and disinfectants.

If chemical disinfectants are to be used they should not be incompatible with any previously-used cleaners.

9.4.1.3 Cleaning and disinfection shall be documented and records retained.

9.4.1.4 The removal of disinfectant and cleaning agent residues from critical surfaces shall be validated.

NOTE Residuals from cleaning agents may need to be removed prior to disinfection.

9.4.1.5 Aseptic processing areas shall be cleaned and disinfected at a frequency which provides appropriate environmental control based on the evaluation of environmental data trends and the assessment of product contamination due to the frequency and nature of aseptic processing.

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

9.4.1.7 The manufacturers' instructions should be followed with respect to storage and use of cleaning agents and disinfectants.

9.4.1.8 Safety regulations shall be considered when selecting cleaning agents and disinfectants and disinfection procedures.

9.4.1.9 Disinfectants and cleaning agents used in the critical processing zone and direct support zones shall be sterile.

9.4.2 Cleaning

The documented cleaning plan shall address at least:

a) approved agents for cleaning, their working dilution, approved storage time and methods for sterilization, where applicable;

b) procedures for cleaning;

c) cleaning aids used, their maintenance and, where applicable, sterilization and storage;

d) time and frequency of cleaning;

e) responsibilities.

9.4.3 Disinfection

9.4.3.1 The documented disinfection plan shall address at least:

a) approved agents for disinfection, their working dilution, approved storage time and conditions, methods for sterilization for ISO 14644-1:1999, Class 5 and Class 7 APAs; a sporicidal agent shall be necessary if environmental monitoring indicates the presence of spore forming organisms, moulds and fungi;

b) procedures for disinfection, disinfectant application, required time of action and employee safety precautions;

c) disinfection aids used, their maintenance and where applicable sterilization and storage;

d) post-disinfection cleaning where required;

e) time and frequency of disinfection;

f) responsibilities.

9.4.3.2 Disinfectant containers shall be labelled with an expiration date.

9.4.3.3 Disinfectant containers shall be cleaned thoroughly and sterilized before use for critical processing zone and direct support zone.

9.4.3.4 Interchanging or rotating disinfectants should be considered.

9.4.4 Equipment used for cleaning/disinfection in APA

9.4.4.1 Equipment used for cleaning/disinfection in the APA shall be of suitable design and approved for use. Equipment in ISO 14644-1:1999, Class 7 or better areas shall be sterilized before use.

9.4.4.2 The intended use in the APA shall be considered and an appropriate evaluation shall be performed. The following characteristics shall be considered for APA use:

a) particle generation (both wet and dry);

b) sterilization compatibility;

c) packaging to ensure sterile transfer into the APA area.

9.4.5 Monitoring of cleaning and disinfection effectiveness

The continued effectiveness of cleaning and disinfection shall be assessed and documented (see 6.8.6).

9.4.6 Effectiveness of disinfection procedures

9.4.6.1 The effectiveness and frequency of application of the disinfection procedure necessary shall be established.

NOTE Validation of disinfectant effectiveness is usually done in laboratory studies demonstrating the capacity of the agents to inactivate inoculated test microorganisms in suspension and in simulated use conditions. Manufacturer's validation reports, if suitably verified, or validation reports of independent testing institutions, can be accepted if it is confirmed to be relevant to the individual manufacturer situation (see EN 1040, EN 1275, EN 13624, EN 13727, prEN 14347, prEN 14348, prEN 14476, prEN 14561, prEN 14562 and prEN 14563.

9.4.6.2 Evaluation of the efficacy of disinfection procedures shall be related to the types and numbers of microorganisms recovered from surfaces before and after cleaning.

9.5 Cleaning, disinfection, and sterilization of equipment

9.5.1 General

9.5.1.1 A cleaning, disinfection and sterilization programme for the equipment shall be established.

9.5.1.2 Cleaning, disinfection and sterilization shall be documented and records retained.

9.5.1.3 Levels of residuals of cleaning agents shall be controlled at defined and justified maximum levels.

9.5.2 Cleaning of equipment

9.5.2.1 Cleaning procedures for critical surfaces shall be established, validated and documented and shall ensure removal of residues to defined levels.

NOTE Residues can interfere with subsequent disinfection and sterilization.

9.5.2.2 Cleaning procedures shall address, e. g.:

a) location where cleaning is to be performed;

b) procedures for disassembly, cleaning and reassembly;

c) approved cleaning agent(s) used including their concentration, volume applied, cleanliness grade or specification, pre-treatment (e.g. sterilization) and approved storage time and conditions;

d) tools to be used (e.g. wipes) including their cleanliness grade or specification, pre-treatment (e.g. sterilization) and storage conditions;

e) measures to protect cleaned equipment or parts thereof from recontamination;

f) specification of cleanliness (e. g. permitted residue limits) to be reached;

g) control measures taken to assure that cleanliness specifications are met.

9.5.2.3 Where cleaning-in-place is used, ISO 13408-4 shall apply.

9.5.3 Disinfection of equipment

9.5.3.1 The effectiveness of the disinfection procedures shall be established.

9.5.3.2 Disinfection shall follow approved methods which shall address at least:

a) procedures for disinfection, disinfectant application, required contact time, post-disinfection cleaning if required and employee safety precautions;

b) approved agents for disinfection, concentration (working dilution), methods for sterilization of the agents, where applicable, approved storage time (expiry dating) and applicable storage conditions;

c) schedule and responsibility for disinfection.

9.5.4 Sterilization of critical surfaces

9.5.4.1 Critical surfaces of equipment shall be sterile.

SIP is the preferred method over disassembly, sterilization and aseptic reassembly.

9.5.4.2 Sterilization procedures shall be validated.

9.5.4.3 Sterilization procedures shall address at least:

a) detailed procedure for disassembly, pre-treatment, sterilization and reassembly, where applicable;

b) type of sterilization process and sterilization conditions to be reached;

c) documented control measures taken to assure that process specifications are met throughout the equipment and all critical surfaces are reached;

d) procedures to protect sterilized equipment or parts thereof from recontamination;

e) storage time and conditions of sterilized components where applicable;

f) procedure and frequency of revalidation measures for the sterilization process.

9.5.4.4 Where sterilization-in-place is used, ISO 13408-5 shall apply

9.5.5 Endotoxin control on critical surfaces

9.5.5.1 Manufacturers shall document the justification of whether it is necessary to control or reduce the endotoxin level for a particular product or product component.

9.5.5.2 When a process is used to reduce the endotoxin level on critical surfaces that process shall be validated to demonstrate a defined reduction in endotoxin level.

9.5.5.3 Adequate cleaning, drying and storage procedures shall be approved to control the defined endotoxin level.

10 Process simulation

10.1 General

10.1.1 Process simulation shall include all parts of the aseptic process and include all aseptic manipulations. It is possible to divide the process into partial operations but all parts of the process shall be simulated. The filter bacterial retentive capacity shall be validated in accordance with ISO 13408-2.

NOTE Process simulation is not intended to validate product sterilization (e.g. the capacity of the sterilizing filter).

10.1.2 For sterile liquids, process simulation shall be conducted using microbiological growth media in lieu of product as the principal method available to assure that the aseptic process is functioning as intended.

For sterile aseptically produced semi-solids, powders, solid materials (including medical devices), microspheres, liposomes and other formulations evaluation by use of traditional liquid media filling may not be possible. In such cases surrogate procedures that represent the operations as closely as possible shall be developed and justified. These procedures may include processing of a sterile surrogate as normal with subsequent immersion in sterile media or some other means of simulation. Sterility of the surrogate shall be determined after its having been subjected to the total aseptic process.

10.2 Media selection and growth support

10.2.1 The microbiological growth media selected for process simulation runs shall be capable of growing a designated group of indicator microorganisms and of supporting microbiological recovery of low numbers of these microorganisms.

NOTE Process simulation is usually conducted with soybean casein digest medium. Media fills when using anaerobic media can be required when obligate anaerobic organisms are isolated from environmental or product samples.

10.2.2 Where surrogate materials such as buffers are used in parts of the process simulation the surrogate material shall not inhibit the growth of the indicator microorganisms.

10.2.3 Verification of growth promotion of media used in specific simulation runs shall be conducted following incubation of the filled units and shall use an appropriate number of units from the run. The incubation temperature for growth promotion tests shall be the same as that used for the media filled units. Growth promotion tests shall be conducted with the organisms specified for sterility test media in the applicable pharmacopoeias. The growth promotion inoculum shall be less than 100 cfu per filled unit.

NOTE 1 Examples of pharmacopoeias include Ph.Eur, JP and USP.

NOTE 2 For complex process simulations it may be necessary to ascertain that the medium samples taken for growth promotion testing are representative of the entire process to ensure that no parts of the process alter the growth promoting properties of the media.

10.3 Simulation procedures

10.3.1 Process simulations shall be conducted under conditions that simulate routine manufacturing procedures and shall as far as reasonably practicable include permissible worst case conditions.

Simulations shall include, e.g.:

a) scheduled hold times and interventions representative of the routine process at the maximum accepted frequency per number of filled units (e.g. weight adjustments, container/closure or product re-supply, sampling or environmental monitoring);

b) frequently occurring unscheduled interventions in representative number and with the highest degree of intrusion acceptable (e.g. corrections for container breakage or tip-over, corrections for leakage of fluid, corrections for stopper jams, correction of line stoppage).

A list of permitted events shall be available. Less frequently occurring unscheduled interventions (e.g. repair or replacement of filling needles/tubes) can be simulated intermittently at a defined and justified frequency.

10.3.2 If multiple sizes of the same container/closure configuration are filled aseptically, representative sizes may be used for initial validation(i.e. bracketing).

NOTE 1 Following initial validation each configuration may be used in a process simulation at a defined frequency.

NOTE 2 Containers with the widest diameter openings and operation at the lowest line speed can represent a worst case due to longest exposure, whereas small containers can represent a worst case due to of lack of container stability in the line operations and the need for increased manual intervention.

10.3.3 Process simulation shall be performed in conjunction with a comprehensive environmental monitoring programme.

10.3.4 The volume filled per container shall be sufficient to wet all surfaces of the containers when swirled or inverted, and provide sufficient head space to ensure capability of microbial growth and to ensure that turbidity can be detected at examination .

10.3.5 The container shall be sufficiently transparent to allow evaluation of turbidity of the contents. If this is not possible the examination shall be by the transfer of the entire contents to a transparent vessel.

10.3.6 For products manufactured routinely under an inert atmosphere, the inert gas shall be substituted with air in the process simulation unless anaerobic simulation is intended.

10.3.7 Units from process simulation should be identified chronologically or otherwise to assist in the investigation should one become necessary.

For lyophilized products process simulation, ISO 13408-3 applies.

10.3.8 Process simulation runs shall be of sufficient duration to cover representative manipulations, interventions and shift changes normally performed in actual processing.

Where the actual aseptic process is interrupted (e.g. during the night and continued the next day) such breaks should also be simulated. Additional environmental monitoring should be included in such cases to ensure that there is no deterioration of the filling environment.

10.4 Incubation and inspection of media filled units

10.4.1 Media filled containers shall be agitated, swirled or inverted before incubation to ensure contact of the media with all interior surfaces in the container .

10.4.2 Units that are leaking, broken or otherwise damaged to the extent that there is no question of their rejection during routine documented visual inspection procedures shall be recorded and removed. Cosmetic defects, non-destructive weight checks and all other units shall be identified and incubated with the other units.

If SOPs clearly describe the disposition of containers exposed during interventions and these are normally discarded then there is no need to incubate such containers produced during process simulation tests. **10.4.3** Media fill evaluation units shall be incubated for not less than 14 days. Incubation temperatures shall be within the range of 20 °C to 35 °C. The use of a specific temperature or temperature range shall be justified and documented.

NOTE If two temperatures are used for incubation, the units are typically incubated for at least 7 days at each temperature (starting with the lower temperature).

10.4.3 After completion of the incubation period the media filled containers shall be visually inspected for the presence of microbial growth in a defined procedure by qualified inspectors.

NOTE Inspection of the units at an earlier time period may be useful to gain a preliminary indication of the results.

10.4.4 Microorganisms isolated from contaminated units shall be identified to species level (genotypic identification methods are recommended) to a level required to assist in the determination of the likely source of the contaminant.

10.5 Initial performance qualification

10.5.1 General

Initial performance qualification shall be conducted for each aseptic processing operation for each line and for each unique product configuration that has not been represented in a previous performance qualification.

10.5.2 Numbers to be filled

10.5.2.1 Sufficient number of simulation units shall be processed (filled) to simulate effectively all activities that are representative of the manufacturing process.

10.5.2.2 The minimum number of simulations and total units are summarized in Table 2.

NOTE It may be necessary to fill more than the minimum number of containers per media fill run in order to accommodate process variables and interventions routinely encountered during production.

10.5.3 Acceptance criteria

10.5.3.1 The aim of any process simulations shall be to achieve zero contaminated units.

NOTE As the aim is to fill sterile product and not to fill product with a low number of contaminated units the filling of a larger number of vials does not result in a higher number of contaminated units which can be accepted.

10.5.3.2 Any contaminated unit shall result in an investigation to determine the cause (if possible).

For acceptance criteria, see Table 2.

10.6 Periodic performance requalification

10.6.1 Scheduling requirements

10.6.1.1 Scheduled process simulation requalification shall be conducted two times annually (approximately every six months) for each aseptic process and filling line. A single filling configuration shall be chosen for each requalification run. The line qualification shall include the activities and interventions representative of each shift and shift changeover.

10.6.1.2 Aseptic filling lines and product/container configurations used less frequently than every six months shall be requalified with an acceptable process simulation test before production is resumed.

10.6.1.3 Requalification of the process or line prior to the scheduled six-month interval should be scheduled in case of significant facility and equipment modification, changes in personnel, anomalies in environmental monitoring results or end product sterility testing. Such changes and requalifications shall be part of the change control process.

10.6.2 Numbers to be filled

The minimum number of runs and total filled units are summarized in Table 3.

NOTE It may be necessary to fill more than the minimum number of units per media fill run in order to accommodate process variables and interventions routinely encountered during production.

10.6.3 Acceptance criteria

10.6.3.1 The aim of the process simulation shall be zero contaminated units.

11.6.3.2 Each process simulation resulting in contaminated units shall be investigated.

10.6.3.3 Acceptance criteria are shown in Table 3.

10.6.3.4 Where contaminated units are found corrective measures shall be taken before the performance qualification is restarted.

10.7 Repeat of initial performance qualification

An aseptic process or filling line shall be subject to a repeat of the initial qualification studies when:

a) requalification of the line failed;

b) production lines have not been in operation for an extended period of time, e.g. one year;

c) there has been a change that has potential to effect the aseptic process.

10.8 Documentation of process simulations

10.8.1 All process simulation runs shall be fully documented. All runs shall include a reconciliation of units processed. Information included with or cross referenced in the records for each process simulation run should be, e. g.:

a) date and time of process simulation;

b) identification of processing area or room used;

c) container/closure type and size;

d) volume filled per container;

e) processing speed;

f) type of media filled;

g) number of units filled;

h) number of units rejected at inspection and the reason for the rejection;

i) number of units incubated;

j) number of units positive;

k) incubation time(s) and temperature(s);

l) procedures used to simulate any steps of a normal production fill, which might include, for example, mock lyophilization or substitution of vial headspace gas;

m) microbiological monitoring data obtained during the media fill set-up and run;

n) list of personnel per shift who participated in the process simulation;

o) growth promotion results;

p) identification of the microorganisms from any positive units;

q) management review;

r) product(s) covered by the process simulation;

s) investigation of runs with a positive unit or failed runs.

10.8.2 Where investigations conclude or suggest a cause of the failure corrective measures shall be implemented.

The effectiveness of the corrective measures should be investigated, where possible, and verified separately before conducting additional runs.

10.9 Disposition of filled product

10.9.1 All product that has been produced on a line subsequent to the process simulation shall be quarantined until a successful resolution of the process simulation has occurred.

10.9.2 In case of a failed process simulation there shall be a prompt review of all appropriate records relating to aseptic production since the last successful process simulation. The outcome of the review shall include justification for the disposition of batches of product affected.