22.3 **FACILITIES**

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

a) wall and floor surfaces which can be cleaned and which resist disinfectants;
b) avoidance of ledges and other horizontal surfaces which could collect particulates or disturb air flow;
c) installation of pipes, ducts and other utilities in a manner to avoid recesses and other surfaces difficult to clean;
d) adequate space for gowning areas, garment storage, soiled garment disposal, and hand washing;
e) separation of gowning and preparation areas from the APA by means of airlocks, pass-through windows for components, supplies and equipment;
f) maintain appropriate pressure differentials required for the given product and process;

22.3.1 The following minimum specification is described for facility design and controls. Additional requirements may be necessary for specific processes. Production of sterile preparations should be carried out in a clean area whose entry should be through airlocks for personnel or for goods. Clean areas should be maintained to an appropriate cleanliness standard and supplied with air which has all been passed through filters of an appropriate efficiency.

22.3.2 There should be separate or defined areas of operation to prevent contamination. For aseptic processing there should be, as appropriate, an air supply filtered through high efficiency particulate air (HEPA) filters under positive pressure and systems for monitoring the environment and maintaining equipment used to control aseptic conditions. Monitoring results should be considered when reviewing batch documentation for finished product release.

22.3.3 In addition equipment for adequate control over air pressure, micro-organisms, dust, humidity and temperature should be provided where appropriate. Air filtration systems, including prefilters and particulate matter air filters, should be used where appropriate on air supplied to production areas.

22.3.4 Processing should be conducted in a cleanroom suite, constructed and operated in accordance with the air cleanliness standards. In order to control the microbiological and particulate cleanliness of the various grades/classes of operation, the areas should be monitored using various methods, eg. volumetric air sampling, settle plates, surface sampling (swabs, contact plates).

22.3.5 The filling of products to be terminally sterilized should be carried out in an appropriate environment for control of viable and non-viable airborne particulate matter. Extra precautions in the form of contained work stations and/or laminar air flow protection may be necessary when solutions intended for intravenous use are filled into wide-necked containers.

22.3.6 Equipment should be designed and installed so that it may be easily cleaned, disinfected or sterilized as required. Exposed surfaces should be smooth, impervious and unbroken in order to minimise shedding or accumulation of particles or micro-organisms and to permit the repeated application of cleaning agents/disinfectants.

22.3.7 Non-sterile products should not be processed in the same area at the same time as sterile products.

22.3.8 Vaccines of dead organisms, or of bacterial extracts, may be filled (after inactivation) in the same premises as other sterile medicinal products. Spore forming organisms should be processed in separate premises or well isolated suites at least until any inactivation stage is completed. Live or attenuated vaccines should be processed and filled in premises separate from other processing or filling operations. Different live vaccines should be processed and filled separately from each other. Separation may be achieved in space or, given adequate cleaning and disinfection, in time. Special isolation facilities may be needed for highly contagious micro-organisms.

22.3.9 The processing of animal tissue materials and of micro-organisms (not required for the current manufacturing process), the performance of test procedures involving animals or micro-organisms, and any animal houses, must be well separated from premises for manufacturing sterile medicinal products, with completely separate ventilation systems, and separate staff.

22.3.10 Where equipment, such as filling equipment, connecting lines, and filter holders, is steam sterilized in autoclaves, it is important that established loading patterns of heat distribution be determined and the ability to achieve sterilization be monitored. One way of ensuring replication of the validated conditions is to follow established loading configuration diagrams and include them as part of the processing record.

22.3.11 Where equipment, such as large tanks and immobile piping is sterilized in place by the passage of pressurized steam, it is important that validation consider temperature and pressure at various locations. This will identify potential "cold spots" where there may be insufficient heat to attain sterility. Some in-line filters in piping systems cause a significant pressure differential across the filter, resulting in a temperature drop on the downstream side. One method of determining if such a drop in temperature will adversely affect the sterilization procedure involves the placement of suitable biological indicators at appropriate downstream locations. Validation could also include measurements of temperature and pressure at various points.

22.3.12 As far as possible, equipment fittings and services should be designed and installed so that maintenance and repairs may be carried out without additional personnel having to enter the clean aseptic rooms. If maintenance must be carried out within these areas, personnel concerned should receive appropriate training in the elements of microbiology and sterile area procedures. When within the areas they should be appropriately dressed, and use tools and equipment which have been sterilized or disinfected. Areas entered for maintenance should be cleaned and disinfected before processing recommences if the required standards of cleanliness and asepsis have not been maintained during the work.

22.3.13 Recording apparatuses should be accurately calibrated on installation and thereafter checked at scheduled intervals.

22.3.14 Validation of equipment performance on installation, is essential. Planned maintenance and frequent checks on performance are also important for critical items of equipment such as sterilizes, air filtration systems, and skills. Checks on steam and hot air sterilizes should include heat distribution and heat penetration studies. Filter efficiency tests should be conducted on air supply systems. Details of maintenance operations and performance checks should be recorded.

22.3.15 When blow/fill/seal units are used, particular attention should be paid to at least the following: equipment design and qualification, validation and reproducibility of cleaning and sterilization, background cleanroom environment in which equipment is located, operator training and clothing, interventions in the critical zone of the equipment, including any aseptic assembly prior to the commencement of filling.

22.3.16 Changing rooms should be designed as airlocks and used to provide physical separation of the different stages of changing and so minimizing microbial and particle contamination of protective clothing. They should be effectively flushed with filtered air. Hand washing facilities should be provided only in the first stage change.

22.3.17 Airlocked doors should not be opened simultaneously. Airlocks should be equipped with interlocks to avoid simultaneous opening of doors.

22.3.18 Control of temperature and relative humidity, if necessary, within defined tolerances and, if possible, monitored continuously.

Aseptic processing facilities shall be designed to promote 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.

22.3.20 **Aseptic Processing Area (APA)**

Access to the aseptic processing area shall be restricted to qualified personnel with sufficient airflow and a positive differential air pressure existing relative to areas outside the APA to prevent contamination of the APA by adjacent areas.

22.3.21 **Processing Zones**

22.3.21.1 **Critical Processing Zones**
Critical processing zones shall be identified, and microbial and total particulate specifications shall be documented. These zones shall contain less than 3 500 particles of $\geq$ 0.5 um per cubic metre of air.

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

All product contact and component sampling sites in the critical processing zone shall be monitored for environmental control during each operational shift.

22.3.21.2 **Other Processing Zones**

Other processing areas shall contain less than 350,000 particles of $\geq$ 0.5 um per cubic metre of air.

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

22.3.21.3 **Non-sterile Support Areas**

Support areas shall contain less than 3,500,000 particles of $\geq$ 0.5 um per cubic metre of air.

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

Personnel in support areas shall wear garments designed to minimize particulate generate, but these garments normally need not be sterile prior to use.

The disinfection and environmental monitoring of this area is less frequent than that utilized for the processing zones.

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

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

22.4 AIR HANDLING SYSTEMS

The basic elements of environmental air systems and control programmes require proper design and control of the aseptic processing facilities including: relative humidity, room temperature, air velocity, HEPA filtration, laminar airflow, and room to room air balance.

22.4.1 Air quality and the monitoring of particulate matter (viable and non-viable) as a means to control physical and biological contamination in the manufacture of injectable products, is one part of the total system of control which should be designed to ensure compliance with the class limits as it applies to areas of manufacture and preparation of product and components. These include filtration though HEPA filters into clean rooms and suitable filtration into critical areas.

22.4.2 In the table below and at the end of this chapter are the basic environmental standards for various operations. These are arranged in classes.

ENVIRONMENTAL REQUIREMENTS FOR SPECIFIC OPERATIONS

OPERATIONS	WORK ZONE (CLASS)	CLEAN ROOM (CLASS)
Compounding and non-sterile filtration of bulk	-----	3
Preparation of containers and closures	-----	3
Washing, drying and depyrogenation of components	-----	3
Filling and sealing of products to be terminally sterilized.	2	3
Aseptic Fill	1/A	1/B
Aseptic Fill in form fill seal machine.	1/A	3
Aseptic addition to sterile manufactured product.	1/A	3

A filtered air supply should maintain a positive pressure relative to the surrounding areas of a lower grade under all operational conditions and should flush the area effectively. Adjacent areas of different grades should have a pressure difference of 15 pascals (guidance value).

22.4.3
It should be demonstrated that air-flow patterns do not present a contamination risk eg. that particles are distributed from a particle-generating person, operation, machine, etc. to a zone of higher product risk.

22.4.4 A warning system should be provided to indicate failure in the air supply. Indicators pressure differences should be fitted between areas where these differences are important. These pressure differences should be recorded regularly.

22.4.5 A determination of airflow patterns shall demonstrate that the airflow is appropriate to the process being performed and shall include investigations with the effects of turbulence which may interfere with the sweeping action of the air. These determinations shall be documented.

Airflow patterns, appropriate to the actual process being performed, should be tested for turbulence that would interfere with the sweeping action of the air.

22.4.6 **HEPA Filter Integrity**

Receipt of HEPA filters shall be accompanied by a supplier's certification that indicates the filter has an efficiency of 99.997% for the retention of 0.3 um or larger particles.

Upon installation, HEPA filters shall be integrity tested by a suitable method. e.g. cold DOP test.

Filters shall be velocity tested periodically, and airflow patterns shall be reassured whenever an airflow configuration change has been introduced. Tests shall be performed in the event of a change in the situation that might affect the integrity of the filter.

22.5 **SANITIZATION AND MONITORING**

22.5.1 Microbiological contamination should be controlled and monitored by appropriate procedures approved by Quality Control.

22.5.2 Cleanrooms and related areas should be cleaned frequently and thoroughly. Non-disposable "sticky mats" should be washed daily. Cleaning activities should be documented as per an approved procedure.

22.5.3 For Aseptic Processing where disinfection is employed to further reduce the surface contamination level, the choice of disinfectants and the way that they are used should be described in a procedure. In addition, detergents, disinfectants and antiseptics should be supplied sterile, or be sterile-filtered or otherwise sterilized at the use-dilution, or be sterilized as a concentrate and diluted only with sterile water. Diluted disinfectants or antiseptics should not be stored. Containers should not be topped up. Disinfectants/detergents used should be validated and approved. When disinfectants are used, more than one type should be employed. Monitoring should be undertaken regularly to detect the development of resistant strains. Disinfectants and detergents used in Class 1 and 2 areas should be sterilised prior to use.

22.5.4 Fogging should not be used as air contaminants are readily dissipated by natural or mechanical ventilation. Fumigation with humidified formaldehyde vapour may be employed to reduce microbiological contamination in places inaccessible to surface disinfection, however if fogging or fumigation is used, the process should be validated.

22.5.5 Cleanrooms and related areas should be monitored at planned intervals for airborne particulate contamination.

22.5.6 Cleanrooms and related areas should also be monitored at planned intervals for microbiological contamination using a combination of "settling plates", surface sampling and air sampling and the results obtained should be used to determine "warning", "action" and "shut-down" levels.

22.5.7 Gowning procedures should be proceduralized and monitored where aseptic filling procedures are practiced.

22.5.7.1 Written gowning procedures, training programmes, monitoring programmes and follow-up procedures shall be established.

At the time of entry into the gowning area, staff shall wear dedicated clothing (eg. plant uniform) and shoes.

Staff should enter the gowning area by way of an airlock.

NOTE: Generally, a mesh hair-net and beard cover, if required, are donned at the airlock. Disposable shoe covers may be used in addition to, or in place of, dedicated shoes.

Employees shall restrict movement in the APA in order to:

a) Avoid unnecessary movements which can generate particles or create turbulence;

b) Avoid reaching across open containers and exposed product and components;

c) Avoid blocking airflow over critical surfaces.

Employees shall regularly check gloves and gowns for proper fit and integrity. Gowned personnel should avoid unnecessary contact with walls, floors and cleaned surfaces with talking among personnel minimized.

Personnel conducting filling operations should not be exchanged during a shift with employees performing other functions within the APA. Operators working in non-sterile support areas shall not have access to the critical processing zone.

22.5.8 Monitoring should be frequent and should take place whilst normal production operations are in progress. In the case of aseptic filling it should provide the basis for the assessment of aseptic hygiene throughout the filling process. Results should be tabulated or graphed and assessed and prompt remedial action taken according to the monitoring standards established. Additional monitoring should be conducted after particular events such as spillages, cleaning, maintenance or fumigation.

22.5.9 Micro-organisms recovered from cleanrooms should be routinely identified, at least to genus level.

22.5.10 In a new unit, with a new process or with new operators, microbial monitoring should be sufficiently intensive to determine patterns and levels of contamination. Once suitable conditions have been established, monitoring may be reduced to a level which will demonstrate maintenance of those conditions.

22.5.11 There should be specific written procedures and documentation for:

- all cleaning and disinfecting of the APA
- Procedures shall include utilization of approved agents, the cleaning schedule, disinfectant application, post-disinfection cleaning if required, and employee safety precautions, including care and storage of cleaning aids. Only cleaning agents and disinfecting agents which have been tested, validated and approved, shall be used.
- the dismantling, cleaning and decontamination of all equipment.
- the cleaning of bulk containers and their subsequent inspection for release for use in processing.
- the control of external contamination of bulk containers during use.
- the assembly of filters and the connecting of hoses and pipelines.

22.5.12 Items brought into cleanrooms, including means of transport, should be of a standard of cleanliness compatible with the environmental standard for the room.
22.5.13 For Aseptic Processing when equipment maintenance or testing has been carried out within a Class 2 or cleaner area, and where the required standards of cleanliness and/or asepsis have not been maintained during this work, the area should be cleaned, and, where appropriate, disinfected and fumigated before processing recommences. This also applies to broth filling procedures which may contaminate the filling area.

22.5.14 The absence of disinfectant and cleaning agent residuals on product contact surfaces shall be confirmed. The manufacturers' instructions should be followed with respect to storage and use. Disinfectants shall be batched with a stated expiration date, and containers should not be refilled. Interchanging or rotating disinfectants should be reconsidered due to potential changes in environmental flora (isolates). A sporicidal agent may be necessary when environmental monitoring indicates the presence of sporeforming organisms, molds and fungi.

The effectiveness and frequency of the disinfection procedure shall be determined as part of the process validation. Evaluation of the efficacy of disinfectants should be related to the reduction of types and numbers of micro-organisms recovered from surfaces during routine environmental monitoring.

22.6 **PERSONNEL TRAINING**

22.6.1 Responsibility for monitoring the processing of sterile products should be delegated by management to a person competent through training and experience in the relevant aspects of microbiology, hygiene and the correct manufacture of sterile products. Only the minimum number of personnel required should be present in the clean area. Personnel involved with maintenance and cleaning should be trained prior to employment and supervised.

22.6.2 Personnel required to work in clean aseptic areas should be selected with care to ensure that they may be relied upon to observe the appropriate discipline and are not subject to any chronic disease or condition which would present an abnormal microbiological hazard to the product. The same principles should be applied to visitors to cleanrooms. Inspections and controls should be conducted from outside the area as far as possible.

22.6.3 All personnel (including those concerned with cleaning, testing and maintenance) should receive regular training in cleanroom procedures and in disciplines relevant to the correct manufacture of sterile products, including hygiene and the basic elements of microbiology.

22.6.4 When external staff who have not received such training (e.g. building or maintenance contractors) need to be brought in, particular care should be taken over their supervision.

22.6.5 Training should be carried out upon recruitment of staff and at regular, planned intervals in accordance with a formal training programme. Records, specific for each member of staff. should be maintained.

22.6.6 Personnel involved in the manufacture of sterile preparations should maintain high standards of personal hygiene and cleanliness and be instructed to report any condition (e.g. diarrhoea, coughs, colds, infected skin or hair, wounds) which may cause the shedding of abnormal numbers or types of contaminants. Actions to be taken about personnel who could be introducing undue microbiological hazard should be decided by designated competent person.

22.6.7 Clothing should be appropriate to the work zone environment in which the personnel will be working. In addition, the following requirements should be adhered to:

·bulky or fluffy personal clothing should be removed before aseptic or cleanroom garments are donned
·wristwatches and jewellery, other than a simple wedding ring should not be worn. Cosmetics which can shed particles should not be used
·beards and moustaches should be covered during the compounding of products
·persons engaged in aseptic processing should wear sterilized or disinfected footwear and should change garments at least every working session

·persons working in Class 2 rooms should wear a single- or two-piece trouser suit gathered at the wrists and with high neck. Headgear must totally enclose hair and beard and be of the helmet/cowl type, tucked into the neck of the suit. Footwear should totally enclose the feet, and trouser-bottoms should be tucked inside the footwear
·sterilize non powdered rubber or plastic gloves, when worn, should be disinfected regularly during operations using a suitable spray and changed at regular intervals or when damaged.

22.6.8 Outdoor clothing should not be brought into the changing rooms associated with clean or aseptic areas, and personnel entering these changing rooms should already be clad in standard factory protective garments. Changing and washing should follow a clearly displayed written procedure.

22.6.9 Clean and aseptic area clothing should be laundered or cleaned and thereafter handled in such a way that it does not gather contaminants which can later be shed. Separate laundry facilities for such clothing are desirable. It should be noted that some methods of sterilization may damage fibres and reduce effective garments. Washing and sterilization operations should follow a clearly displayed written procedure.

22.6.10 For each worker in a class 2 room, clean, sterile, protective garments should be provided at each work session.

22.7 **MANUFACTURING REQUIREMENTS AND CONTROLS**

22.7.1 Starting materials should be selected so as to contain only minimal quantities of micro-organisms or pyrogenic material. The material specification should include requirements for microbial monitoring. with limits as necessary.

22.7.2 Precautions should be taken during all processing stages, before and after sterilization to avoid contamination of the product with micro-organisms.

22.7.3 Activities and conversation in clean and aseptic areas should be kept to a minimum. Movements of personnel should be controlled and methodical, so as to avoid excessive shedding of particles and organisms due to over-vigorous activity and to avoid disruption of air flow patterns.

22.7.4 Containers and other materials liable to generate particles or fibres should not be taken into areas of Class 1 or Class 2.

22.7.5 The intervals between the washing and drying and the sterilization of components and equipment should be as short as possible and subject to a time limit appropriate to the storage conditions. The interval between sterilization and use of these materials should also be subject to a time limit.

22.7.6 Articles required in an aseptic area should be sterilized and passed into the area in such a way which will avoid contamination of the area.

22.7.7 The time between the start of the preparation of a solution and its sterilization (or sterile filtration) should be as short as possible and subject to a limit for each product that takes into account its composition and the prescribed method of storage.

22.7.8 Unless special storage precautions are taken, bulk solutions should have no greater volume than can be filled in one working day and should be filled into final containers and sterilized within one working day.

22.7.9 The microbiological load of products should be as low as practicable prior to sterilization eg. all solutions should be passed through a bacteria-retaining filter immediately before filling.

22.7.10 Each procedure used for the sterilization of a particular quantity or volume of a material, component, or product should have been demonstrated to be effective and reliable by suitable validation studies.

22.7.11 Batch processing records for sterile products should include details of the sterilization of the components and equipment used.

22.7.12 Water treatment plants should be designed, constructed, and maintained to ensure the reliable production of water of the required quality. They should not be operated beyond their designed capacity. The water should be produced, stored and distributed in such a manner as to discourage microbial growth (eg. by constant circulation at temperatures above 70°C, and avoidance of places where water may remain stagnant such as U-bends, 'dead ends' and ill-designed valves).

22.7.13 Water sources, water treatment equipment and treated water should be monitored regularly for chemical, microbial and pyrogen contamination as relevant. Records should be maintained of the results of the monitoring, and of any remedial action.

22.7.14 Unsterilized distilled water intended for further processing or sterilization should not stand for more than a short time unless special precautions are taken, such as storage above 65°C, to prevent both the growth of bacteria and the consequent development of pyrogens.

22.7.15 Where water or solutions are held in sealed vessels, any pressure relief outlets should be protected by hydrophobic microbial air filters.

22.7.16 Components and containers should be handled after the final cleaning process in such a way that they are not subject to recontamination. The final rinse should be with purified water of appropriate quality.

22.8 VALIDATION OF ASEPTIC PROCESS

22.8.1 Aseptic processing and filling equipment, used in aseptic work procedures and environments should be validated for their overall performance at the time of qualification and at regular intervals thereafter by test runs in which suitable sterilized agents which will not inhibit microbial growth are passed through the routine procedures up to the sealing of filled final containers. In the case of liquid processing the test agent should be soybean-casein digest medium and the filled sealed containers should be incubated for at least 14 days at 3± 2 °C. When appropriate to the product, other media or temperatures may also be used. In the case of solid or semisolid processing, a process should be developed to imitate the filling operation as closely as possible. Full microbiological test controls should be carried out.

22.8.2 For each container type, at least 3 000 typical containers should be filled to the labelled quantity and sealed in an undivided test run. The test run should be carried out immediately after a regular production run and in "worse case" conditions. No growth should be observed in the incubated containers, but production may continue if not more than three containers show evidence of microbial growth after incubation (i.e. contamination rate of not more than 0,1 %).

22.8.3 Initial validation should employ at least three runs, which should not be continuous, but consideration should also be given to employing more than 3 000 units in subsequent runs in order to reach statistical significance in estimating the contamination rate.

22.8.4 Continuing validation should occur at least twice per year for each shift for each filling/sealing line. All personnel should take part in a media fill at least once per year. The duration of the run should be sufficient to cover all manipulations that are normally performed in actual processing at filling rates comparable to standard Production.

22.8.5 Medium should be made to contact the entire inside surface of the containers being filled at intervals during the incubation period, e.g. by swirling or tumbling. Media fertility and stasis tests should be carried out.

22.8.6 Consideration should be given to validating the ability of the medium used to grow micro-organisms recovered from environmental monitoring or from sterility testing.

22.8.7 When a new aseptic process is introduced, when any significant change is made in such a process or in the equipment, when staff are being trained and at regular intervals thereafter, the efficacy of

aseptic procedures should be validated, eg. by filling a sterile liquid nutrient medium or powder and testing for the incidence of contamination. Such fillings should be carried out under normal operating conditions.

22.8.8 Procedures shall be in place describing the operations of all critical equipment. The qualification of equipment generally includes calibration, installation qualification (IQ), operation qualification (OQ), and performance qualification (PQ).

22.8.9 Processing equipment such as sterilizers, component washers, filters, fillers, closure placement equipment, sealing machinery, and lyophilizers shall be qualified as part of the overall programme. Product contact surfaces shall be sterilized and process validated.

22.8.10 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.

22.8.11 The following measures should be addressed for steam-in-place systems:

a) displacement and elimination of entrapped air;
b) constant bleeds or steam traps at all low points to eliminate condensate buildup;
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.

22.9 STERILIZATION PROCESSES

22.9.1 General

22.9.1.1 Sterilization can be affected by moist or dry heat, by ethylene oxide (or other suitable gaseous sterilizing agent), by filtration with subsequent aseptic filling into sterile final containers, or by irradiation with ionizing radiations (but not with ultraviolet radiation). Each method has its particular applications and limitations. Where possible and practicable, heat sterilization is the method of choice.

22.9.1.2 For effective sterilization, the whole of the material must be subjected to the required treatment, and the process must be designed and monitored to ensure that this is achieved.

22.9.1.3 Before any sterilization process is adopted, its suitability for the product and its efficacy in achieving the desired sterilizing conditions in all parts of each type of load to be processed should be confirmed. Such validation should be repeated at suitable scheduled intervals and whenever significant modifications have been made to the equipment. Records should be kept of the results.

22.9.1.4 Products which are intended to be sterile, should be preferably heat sterilized in final sealed containers. Each cycle of heat sterilization should be monitored by means of temperature probes to determine if the heat distribution in the sterilization vessel is uniform.

22.9.1.5 The charts of automatic recorders of cycle parameters should constitute part of the batch processing records of sterile products and should be marked to identify the batch or batches to which each applies.

22.9.1.6 Each separate sterilizing basket, package, pallet etc., of products or components undergoing sterilization should be fastened to ensure its integrity and should bear in a conspicuous position a visual indicator to demonstrate whether or not it has passed through a sterilization cycle.

22.9.1.7 To verify the continuing effectiveness of dry heat sterilizing cycles, suitable microbiological indicators of known high resistance to the dry heat sterilization process should be included in sterilizing cycles and placed at representative locations in typical loads. The indicators should be located in the most difficult-to-sterilize site within the sterilizer and, where appropriate, within the product.

22.9.2 **Moist Heat**

22.9.2.1 This method is suitable only for water-wettable materials and aqueous solutions. Other materials must be sterilized by other methods.
22.9.2.2 Moist heat sterilization is achieved by exposure to saturated steam under pressure in a suitably designed chamber. Under these conditions there is an exact relationship between steam temperature and pressure, but the pressure is used solely to obtain the temperature required and otherwise contributes nothing to the sterilization process. The temperature and not the pressure must be used to control and monitor the process.

22.9.2.3 Whilst temperatures and periods of treatment are recommended in official compendia, (eg.121 °C for 15 minutes), other combinations of temperature and time can be used provided they have been validated. It is important to recognize that the temperature-time relationship is complex, that at temperatures below 115 °C disproportionately long periods of time are required, and that as temperature is reduced, the process may become progressively less reliable.

22.9.2.4 Items to be sterilized (other than aqueous medicinal products in sealed containers) should be wrapped in a material which allows removal of air and prevents penetration by micro-organisms after sterilization. All parts of the load should be in contact with water or saturated steam at the required temperature for the required time.

22.9.2.5 Unless special precautions are taken, air must be displaced from the chamber, and from materials within the chamber, either by a period of free steaming before the sterilization cycle begins or by use of a vacuum pump.

22.9.2.6 Mixtures of steam with air may be used for sterilizing sealed containers of aqueous fluids provided that steps are taken to ensure homogeneity of the steam-air mixture throughout the chamber, and the process has been validated.

22.9.2.7 Sufficient time must be allowed for the whole of the load to reach the required temperature before measurement of the sterilizing time-period is commenced. This time must be determined for each type of load to be processed before the method is adopted.

22.9.2.8 Care should be taken to ensure that steam used for sterilization is of suitable quality and does not contain additives at a level which could cause contamination of product or equipment.

22.9.3 **Dry Heat**

22.9.3.1 Dry heat is suitable for sterilizing equipment, non-aqueous liquids and other materials which can withstand the temperatures required. Various combinations of temperature and time are recommended in official compendia but other combinations of temperature and time can be used provided they have been validated.

22.9.3.2 Heating should be carried out in an oven or other equipment which will achieve sterilizing conditions throughout the load. The method of loading used should not be such as to lead to an uneven temperature distribution.

22.9.3.3 Before the timed sterilization period begins, sufficient time must be allowed for the temperature of the whole load to reach the requisite level. This time should be determined for each type of load to be processed, and the timed sterilization period should not start until the entire load is known to have reached that level .

22.9.4 **Filtration Sterilization**

22.9.4.1 Sterilization by filtration should only be employed when heat sterilization cannot be applied because of its detrimental effect on the active ingredients.

22.9.4.2 Solutions or liquids can be sterilized by filtration through a sterile filter of nominal pore size of 0,22 micron (or less), or with at least equivalent micro-organism retaining properties, into a previously sterilized container. Such filters can remove bacteria and moulds but not all viruses or mycoplasmas.

22.9.4.3 The integrity of the filter assembly should be checked by an appropriate method, such as a bubble-point pressure test or forward-flow pressure test immediately before and after use. Abnormal filtration flow-rates should be noted and investigated. Results of these filter-integrity checks should be recorded in the batch record.

22.9.4.4 Any potentially fibre or particle releasing filter should be followed by a downstream non-fibre releasing filter that will retain such particles.

22.9.4.5 If it is intended to use a filter for an extended period, the effectiveness of the process should be validated, taking into account such aspects as the microbial content of the solution, the capacity and efficacy of the filter and its housing, and the potential for growth of organisms on or through the filter. It is preferable not to use the filter for longer than one working day.

22.9.4.6 Due to the potential additional risks of the filtration method as compared with other sterilization processes, a second filtration via a further sterilized micro-organism retaining filter, immediately prior to filling, may be advisable.

22.9.4.7 The time interval between sterilizing a bulk solution by filtration and filling it into final containers should be kept to a defined minimum, appropriate to the conditions under which the filtered bulk is stored.

22.9.4.8 Filters should not adversely affect the quality or content of solutions by removal of ingredients from them or by release of substances into them. Asbestos filter pads should not be used for filtration of parenteral products. Filters should be treated as starting materials and subjected to quality control. Filters must be sterilized when aseptic filling is carried out.

22.9.4.9 Any new or modified filtration system for sterilization should be validated for integrity before it is placed in service and a record of such validation kept. Only positive pressure filtration should be employed.

22.9.4.10 Where the bulk batch is divided into lots for different sterilization or lyophilisation cycles, all such lots should be distinguishable from one another, by label and in the records.

22.9.5 **Biological Indicators**

22.9.5.1 Biological and chemical indicators used alone are not acceptable as proof of sterility.

22.9.5.2 Biological indicators (i.e. preparations of bacterial cultures, usually spores of selected resistant strains) are much less reliable than physical monitoring methods (except in ethylene oxide sterilization).

22.9.5.3 Strict precautions must be taken when handling biological indicators due to the hazard of introducing potential contaminants into an otherwise microbiologically clean area.

22.9.5.4 Microbiological indicators should be treated as starting materials and subjected to quality control.

22.9.6 **Chemical Indicators**

22.9.6.1 Chemical indicators are available for heat, ethylene oxide and radiation sterilization, usually in the form of adhesive tapes or patches, colour spot cards, small tubes or sachets. They change colour as a result of chemical reaction brought about by the sterilization process, but it is possible for the change to take place before the sterilizing time has been completed, and hence, with the exception of plastic dosimeters used in radiation sterilization, they are unsuitable as proof of sterilization.

22.9.6.2 Certain other substances with melting points which coincide with the sterilization temperature may be used as indicators in heat sterilization. They indicate that the temperature has been reached, but not that it has been maintained, or for how long.

22.9.6.3 Radiation-sensitive colour discs, not to be confused with plastic dosimeters, are used to differentiate between packages which have been subjected to irradiation and those which have not. They are not indicators of successful sterilization, and the monitoring of radiation sterilization by calibrated plastic dosimeters is the only way of ensuring that the sterilizing dose has been given.

22.9.7 **Ethylene oxide**

22.9.7.1 This method should only be used when no other method is practicable. During process validation it should be shown that there is no damaging effect on the product and that the conditions and time allowed for degassing are such as to reduce any residual gas and reaction products to defined acceptable limits for the type of product or material.

22.9.7.2 Direct contact between gas and microbial cells is essential: precautions should be taken to avoid the presence of organisms likely to be enclosed in material such as crystals or dried protein. The nature and quantity of the packaging materials can significantly affect the process.

22.9.7.3 Before exposure to the gas, the material should be brought into equilibrium with the humidity and temperature required by the process. The time required for this should be balanced against opposing need to minimise the time before sterilization.

22.9.7.4 Each sterilization cycle should be monitored with suitable biological indicators appropriately distributed through the load. The information so obtained should form part of the batch record.

22.9.7.5 Records should be obtained of the time taken to complete the cycle, the pressure, temperature and humidity within the chamber during the process, the gas concentration and total amount of gas used. The pressure and temperature recorded during the cycle should form part of the batch record.

22.9.7.6 After sterilization, the load should be stored in a controlled manner under ventilated conditions to allow residual gas and reaction products to be reduced to defined validated levels.

22.9.8 **Radiation**

22.9.8.1 Radiation sterilization is used mainly for sterilization of heat sensitive materials and products.

22.9.8.2 During the sterilization procedure the radiation dose should be measured. For this purpose dosimetry indicators which are independent of dose rate should be used, giving a quantitative measurement of the dose received by the product itself. Dosimeter absorbance should be read within a short period after exposure to radiation.

22.9.8.3 The total radiation dose should be administered within a predetermined time span.

22.9.9 **Air Removal**

The removal of air from a steam-in-place system may be accomplished by one of two methods:

a) by gravity
b) through the use of vacuum

22.9.10 **Condensate Removal**

Condensate should be continuously removed from all low points to maintain sterilization conditions in the system.

22.9.11 **Post-sterilization system integrity**

System integrity shall be maintained after sterilization. The system should then be purged of steam and condensate and maintained under positive pressure until ready for use.

NOTE 15: The introduction of gas can dry the system prior to use, which is very important if the product to be processed is non-aqueous.

22.9.12 **Depyrogenation**

Data should be available that demonstrates a knowledge of the (or endotoxin) loading on components prior to treatment in a depyrogenation process. When a depyrogenation process is used, the data shall demonstrate that the process will remove a greater quantity of endotoxin than may have been originally present in the component or product.

NOTE: Plastic medical devices and/or containers may be depyrogenated by rinse processes, and/or high temperature moulding, and/or extrusion processes prior to filling. Rubber compound stoppers may be rendered pyrogen-free by multiple cycles of washing and rinsing prior to final steam sterilization. The final rinse should be water-for-injection quality.

22.9.13 **Gases**

Compressed air shall be dry and oil-free. All compressed gases that contact products, container/closures or product contact surfaces shall be filter sterilized.

22.9.14 **Processing Time**

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. Elapsed time between component washing and sterilizing should be minimized.

22.9.15 **Sampling**

All product contact and component sampling sites in the critical processing zone shall be monitored for environmental control during each operational shift. If the environmental control programme indicates that specified limits are exceeded, corrective action shall be taken in accordance with written procedures.

Other processing zones shall be monitored frequently, with sampling frequency based on classification of the zones and testing data.

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

Support areas shall be routinely monitored, but may be monitored on a less frequent basis than processing zones.

22.9.15.1 **Sampling Sites**

Sampling sites should be derived from and consistent with those used during validation activities. The individual sampling sites for each programme should be at the discretion of the manufacturer reflecting differences in facility/equipment design and processing parameters.

22.10 **QUALITY CONTROL**

22.10.1 **Sterility Testing**

22.10.1.1 A test for sterility must be carried out on samples from each batch of sterile products except for products for which approval to omit the test for sterility has been specifically granted by the inspecting authority.

22.10.1.2 Where a batch of product is sterilized as a series of lots, each of which is subjected to a separate sterilizing cycle or is subjected in processing to different treatment which may affect its sterility, eg. different lyophilisation cycles, each lot should be tested for sterility.

22.10.1.3 Samples for the test of sterility should be taken:

· in the case of aseptically prepared products, at regular intervals during the filling operation so as to be representative of the whole of the batch or filling session. In particular the samples should include containers filled at the beginning and end of the batch and after any significant interruption of work. Resampling for retesting must follow the same principle. Where possible, the first and last units filled should be part of the initial sample from all prescribed locations and at all prescribed times . These should be divided between test samples and retention samples.

·records should be kept of the results of all sterility tests and control tests. Contamination rates for different products and for different sterility test techniques should be calculated periodically and compared, and their significance assessed.

· for products which have been heat sterilized in their final containers, consideration should be given to taking samples from the potentially coolest part of the load.

22.10.2 **Pyrogen Testing**

22.10.2.1 The water used in the preparation of sterile products should be tested for pyrogens at least once per week and after any repair or disturbance to the system, using, for example the limulus amoebocyte lysate test. Sampling should include "worst case" situations, including start-up. Water for injection stored below 65 °C should be tested at least twice weekly for microbial and pyrogen contamination.

22.10.2.2 Appropriate samples for pyrogen testing should include those taken from the first units filled, the last units filled, the first units filled immediately following a break in the filling line (eg. a filter change) and the first units filled following prolonged downtime periods, i.e. one hour or more.

22.10.3 **Media Fills**

Media filling in conjunction with comprehensive environmental monitoring of the aseptic area can be particularly valuable in evaluating the aseptic processing of sterile products. The media fill should simulate the aseptic process as far as reasonably practical.

Scheduled media fill requalifications shall occur at least every six months for each aseptic process and filling line. The media fill run shall be of sufficient duration to cover all manipulations normally performed in actual processing. Media fill evaluations shall be incubated for at least 14 days at temperature ranges of 20-25 and 30-35. Requalification acceptance criteria shall meet the number of runs and total filled units which is summarized as follows:

a) For production batch sizes of less than 500 units, 3 media fill runs of the maximum batch size shall be conducted.

b) Alternatively, for small production batch sizes where infrequent batches (less than 4 per year) are filled, or for clinical batches, it shall be acceptable to requalify the process of 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.

c) For production batch sizes between 500 and 2,999 units 1 media fill run of at least the maximum batch size shall be conducted.

d) For production batch sizes greater than 3 000 units, 1 media fill run of at least 3 000 units shall be conducted.

Guidance values for microbiological monitoring of clean rooms in operation

	Maximum number of viable organisms (a)			
GRADE	air sample cfu/m^3	settle place (90mm) cfu/4 hour	contact place (55mm) cfu	glove print 5 fingers cfu
A	< 1 (b)	< 1 (b)	< 1 (b)	<1 (b)
B	10	5	5	5
C	100	50 (c)	25	-
D	200	100 (c)	50	-

Notes:

(a) Recommended limits for contamination may be exceeded on isolated occasion and require only an examination of the production conditions and the control system. If the frequency is high or shows an upward trend then action should be taken.

(b) Low values involved here are only reliable when a large number of samples is taken.

(c) For Grades C and D settle plates may be exposed for less than 4 hours.

Grade	Examples of operations
A	Aseptic preparation and filling. Filling of products to be terminally sterilized when products are unusually at risk.
B	Transfer and storage of containers of freeze-dried products and components for aseptic filling.
C	Preparation of solutions and components for subsequent sterile filtration and aseptic filling. Preparation of solutions and components for subsequent filling and terminal sterilization when products or components are considerably exposed or unusually at risk. Filling of products to be terminally sterilized.
D	Preparation of solutions and components for subsequent filling and terminal sterilization.

22.11 FINISHING OF STERILE PRODUCTS

22.11.1 Ampoules should be sealed by a "drawing-off" technique rather than by tip-sealing.

22.11.2 Containers sealed under vacuum should be tested for maintenance of that vacuum after an appropriate, pre-determined delay.

22.11.3 Filled containers of parenteral products for administration to humans should be inspected individually. When this inspection is visual it should be done under suitable controlled conditions of illumination and background. Operators doing the inspection should pass regular eye-sight checks, with spectacles if worn, and be allowed adequate breaks from inspection.

22.11.4 Where automatic/electronic/photo-electric methods of inspection are used, the effectiveness of the equipment should be validated and its sensitivity monitored.
22.11.5 Tests to demonstrate the integrity of seals of closures on product containers should be carried out during the production of each batch. These results should form part of the batch processing records.

22.11.6 Wherever the nature of the product makes it possible, every filled and sealed container of parenteral product should be tested for physical defects and for particulate contamination.

22.11.7 It is appropriate to monitor and control the microbiological content of the water and other materials used in the leak test procedure.

22.12 BATCH RELEASE

22.12.1 The decision to release a batch of sterile product for use should take account of not only the specific production records and results of tests performed on that batch, but also the cumulative test records and information gathered from the monitoring of the environment, personnel, intermediate products, equipment and processes, both before and during the manufacturing of the batch.

CHAPTER 23

ISOLATOR TECHNOLOGY

23.1 PRINCIPLES

23.1.1 Isolator technology is now widely used and accepted for the aseptic processing of pharmaceuticals. The use of barrier systems offers improvements in the handling of pharmaceutical products in circumstances where product protection and the maintenance of asepsis, and/or operator protection and the control of hazardous substances are critical requirements. Isolators have several advantages over conventional clean rooms and laminar flow cabinets for aseptic preparation and dispensing of injections. Isolators provide an acceptable level of sterility assurance for aseptic operations. Isolators cannot be regarded as totally sealed units since access to the controlled workspace must be open when materials are transferred into and out of this area and the workspace is continuously supplied with HEPA filtered air. Other than this air supply, the controlled workspace of the isolator will, when in use, be sealed from its background environment.

23.1.2 Critical SOP's include those detailing sanitisation, introduction of material, withdrawal of material, and training of personnel.

23.2 DEFINITION OF TERMS

23.2.1 Isolator

A containment device which utilises barrier technology for the enclosure of a controlled workspace.

23.2.2 Type 1 Isolator

An isolator primarily designed to protect the product from process-generated and external factors that would compromise its quality.

23.2.3 Type 2 Isolator

An isolator designed to protect the product from process-generated and external factors that would compromise its quality and to protect the operator from[n hazards associated with the product during operation and in the event of failure.

23.2.4 Air lock

An enclosed space with two or more doors and which is interposed between the controlled workspace and the background environment of the isolator, for the purpose of controlling air flow between them and to facilitate the transfer of materials between them.

23.2.5 Alarm

An audible and/or visible signaling system which warns of a fault condition. It must incorporate a device to ensure that it cannot be cancelled until corrective action is taken.

23.2.6 Background Environment

The environment in which the isolator is sited. Background environments are categorised in table 3.

23.2.7 Controlled Work Space

An enclosed space constructed and operated in such a manner and equipped with appropriate air handling and filtration systems to reduce to a pre-defined level the introduction, generation and retention of contaminants within it.

23.2.8 Critical Zone

That part of the controlled workspace where containers are opened and product is exposed. Particulate and microbiological contamination should be reduced to levels appropriate to the intended use.

23.2.9 Decontamination

A process which reduces contaminating substances to a de-defined acceptance level.

23.2.9.1 Sanitisation

That part of decontamination which reduces viable micro-organisms.

23.2.9.2 Particulate Decontamination

That part of decontamination which reduces visible and sub-visible levels to a defined acceptable level.

23.2.9.3 Chemical Decontamination

That part of decontamination which reduces chemical contamination to a defined acceptance level.

23.2.10 Docking Device

A sealable chamber which can be (completely removed from or locked onto an isolator and then opened without contamination passing into, or out of, the controlled workspace or the chamber.

23.2.11 Exhaust Filter

A filter through which the exit stream of air from an isolator

23.2.12 HEPA (High Efficiency Particulate Air) Filter

Filters with no greater than 0,003 % penetration of 0,5 um particles when tested according to BS 3928.

23.2.13 Laminar Flow

Airflow in which the entire body of air within a confined area moves with uniform velocity along parallel flow lines.

Note: May also be referred to as "unidirectional flow'.

23.2.14 Sterilisation

The process applied to a specified field which inactivates viable micro-organisms and thereby transforms the non-sterile field into a sterile one.

23.2.15 Transfer Chamber
A device which facilitates the transfer of goods into or out of the controlled workspace whilst minimising the transfer of contaminants.

23.2.16 Transfer Hatch

See Transfer Chamber.

23.2.17 Transfer Isolator

A separate isolator which can be fixed or removable and which is attached to the main operational unit, acting as a complete transfer device.

23.2.18 Transfer Device

A device, which can be fixed or removable, which allows materials to be transferred into or out of the controlled

23.2 19 Transfer Port

See transfer chamber.

23.2.20 Transfer System

The process of transfer of materials into and out of the isolator through a transfer device.

23.2.21 Turbulent Flow

A flow of air which is non-laminar.

23.3 ISOLATOR DESIGN PRINCIPLES

Although the specifications should not be restrictive, there are basic design parameters to which isolators should conform.

23.3.1 Air input may be laminar flow, turbulent flow, or a combination of the two.

23.3.2 The critical zone of the controlled workspace should be equivalent to the EC Grade A, but the airflow in the critical zone need not be laminar flow (see 23.3.3).

23.3.3 If the isolator is not supplied with a laminar air flow system, tests should be performed so as to confirm that only air complying with the requirements of EC Grade A is applied to the critical zone. Air should be effectively swept from the controlled workspace and startling vortices. Stagnant areas should not exist.

23.3.4 Type 2 isolators should operate under negative pressure.

23.3.5 Type 2 isolators for use with radiopharmaceuticals should incorporate an appropriate radiation protective system against ionising radiations.

23.3.6 For operator protection, in the event of a breach in type 2 isolators a minimum breach velocity of O,7m sec- should be maintained.

23.3.7 The transfer of materials into and out of the controlled workspace is a critical factor of the isolator's operation. The transfer device separates the background environment from the Grade A controlled workspace. It should be designed such that it does not compromise the Grade A controlled environment. To this end an interlocked device will provide greater security. The size of the transfer device should be sufficient to allow all necessary materials and equipment to be passed through

Note: Commissioning studies should include tests to confirm that contaminants will not pass from the transfer device into the controlled work area. A fully validated transfer procedure should be in place.

23.3.8 All internal surfaces (including seals, holes, screws) should be accessible to the operator for cleaning and disinfection purposes without compromising the isolator's integrity. They should be resistance to corrosion by cleansing and disinfecting agents and should be capable of withstanding gaseous disinfection or sterilisation.

23.3.9 The pressure differential between the Grade A controlled workspace and the background environment should be continuously monitored.

23.3.10 All filters in isolators in which hazardous substances are handled must have a safe change facility. Both the manufacturer and the user should be made aware of the risks associated with changing filters.

23.3.11 All exhaust (or re-circulated) air should pass through one or more HEPA filters. Extract air from type 2 isolators should normally be ducted to the outside through one or more HEPA filters and another necessary absorption media (eg. carbon). Where isolators are used infrequently or low levels of hazardous materials are handled, then the exhaust air may be re-circulated into the background environment through two HEPA filters in series provided the risk has been assessed and has been shown to be low risk. (For further details of exhaust filters see also appendix 5.)

23.3.12 When designing isolators, consideration should be given to optical clarity, lighting, noise levels, humidity, electrical safety, temperature, vibration, ergonomics and the comfort of the operator (s),

23.3.13 Pressure differentials and the direction of air flow should be such that when the access between the transfer system and the controlled workspace is open, contaminants will not pass into the controlled workspace and, additionally in type 2 isolators, operator protection is also maintained.

23.3.14 If a fixed transfer device has its own air supply it should be HEPA filtered.

23.3.15 The air change rates in all parts of the isolator system should be sufficient to maintain the defined grade of environment

Note: The air change rate will be such that any unfiltered air that enters the isolator or transfer device will be purged from the system within 5 minutes.

23.3.16 The fan should not be capable of damaging the filters in their maximum loaded state.

23.3.17 Isolators should have the facility to enable routine leak testing and particle counts to be carried out in the isolator itself and in its transfer devices. Where access points are provided for test equipment they should be labelled.

23.3.18 The isolator should be designed so that the HEPA filters can be integrity tested in situ.

23.4 THE SITING OF ISOLATORS

23.4.1 Isolator(s) should be sited in a dedicated rooms(s) used only for the isolator and its ancillary equipment and related activities. The interior surfaces of the rooms (walls, floots, ceiling) should be smooth, free from cracks and open joints. They should not shed particulate matter and should allow easy and effective cleaning and sanitisation.

23.4.2 The classification of the background environment in which the isolator is located will depend upon the design and, operational characteristics of the isolator, but should be at least grade D. When deciding on the siting of isolators, consideration should be given to the following:
The type of isolator - type I/type 2.
The transfer system - see appendix 1.
The level and frequency of use i.e. dispensing/ preparation/manufacture.

In order to address these variables, isolators have been classified according to the transfer system. Details of the different transfer systems and the corresponding transfer devices are shown in appendix 1. The background environment for the isolator can then be categorised as I, II, III, IV, V or EC Grade A-D depending upon the transfer system and the use to which the isolator will be put (tables 1 and 2).

23.4.3 The definitions of air quality categories I-V are given in table 3. The categories have been defined according to their permitted levels of viable and non viable particles. For comparative purposes, the requirements of the different environmental classifications from commonly quoted standards documents are also included in the table.

It should be noted that the levels of viable micro-organisms for categories II-IV of the background environment are more stringent than then nearest grade of air quality specified in the EC GMP.

23.4.4 For pharmaceutical applications the major criterion upon which the background environment is categorised should be the risk of microbiological contamination of the product. For this reason the environment has been classified in this document according to the number of viable organisms that can be detected.

It is recognised however that environmental testing is not a guarantee that environmental quality is maintained.
Procedures and quality systems should be used to provide the necessary level of quality assurance.

23.5 FACTORY ACCEPTANCE TEST (FAT)

23.5.1 A factory acceptance test (FAT) should be performed. The report should cover at least a check against Customer Order for completeness, visual check for appearance and identification, the record of serial numbers of filters, dimensional check, electrical installation and safety check, functional check, including operation of interlocks and alarms and documentation dossier.

23.6 INSTALLATION QUALIFICATION (IQ)

23.6.1 Qualification data (records) of the isolator should at least cover installation qualification (IQ), i.e. integrity and leakage test, filter integrity test, filter mounting integrity test, instrument check and calibration as well as functional check of all operating systems.

23.7 OPERATIONAL QUALIFICATION (OQ)

23.7.1 Operational qualification (OQ) should be performed.

23.7.2 Records should cover checks on air flow rates, pressures controlled within specified limits, air flow patterns, temperature and humidity patterns, particle counts as well as noise and light levels.

23.7.3 Testing of filters and filter housings should be done at regular intervals.

23.7.4 The vibration effects of HVAC fans and filling equipment on joints and particularly on hepa filter clamping systems should be tested. Maximum limits for vibration should be set, monitored and controlled.

23.7.5 The ventilation/filtration system should be appropriate for functions performed in the isolator and should be validated.

23.7.6 Leak tests of the Isolator should be performed on a regular basis, including the glove/sleeve system.

23.8 PERFORMANCE QUALIFICATION (PQ)

23.8.1 Performance qualification (PQ) should be performed.

23.8.2 Sterilisation cycles with standard loadings should be developed and validated.

23.8.3 There should be relevant SOP's with respect to operations being performed.

2 3.9 MICROBIOLOGICAL MONITORING

23.9.1 General

Viable particle monitoring for micro-organisms and non-visible particle monitors should be performed at regular intervals.

A plan of the isolator should be prepared with coded positions for settle plate, swabbing and air sampling sites. The following methods may be employed:

23.9.2 Settle Plates
Coded and dated, sterile, tryptone soya agar plates should be exposed for two hours at all test sites within the isolator. These should be incubated in accordance with a written SOP at the appropriate temperature for up to five days, or as otherwise chosen by the microbiologist.

23.9.3 Surface Samples
Surface samples at coded sites using sterile contact plates or sterile moistened swabs should be taken

Note: Each sample site should be sanitized to remove any material transferred to it during the sampling process.

23.9.4 Active Air Sampling

Samples should be taken at the coded sites.

Where the test utilises standard plates or strips, these should be incubated at the appropriate temperature for up to five days.

The point during the production process that finger dabs should be carried out should be defined eg. at a break time or end of a day's work, in accordance with a written SOP

23.9.6 Broth, or Media Fills (Media Process Simulation)

The broth fill is a validation procedure that challenges both operator and facilities. The purpose of broth fills is to simulate routine aseptic operations in such a way as to produce broth filled units that can be tested for microbiological contamination.

The number of units filled should represent a normal batch size.

Incubate at the designated temperature for up to 14 days. If the final container is part filled to ensure all surfaces are in contact with broth at some stage during incubation.

A procedure should define actions following positive results and should focus initially on whether the facility/equipment or operator practices are failing.

Note: The type of broth used is often sterile tryptone soya broth that may be presented in double strength to allow for dilution with buffer, saline, or water to simulate the process. Any suitable liquid

culture medium may however be used but the ability of the broth to support growth should be demonstrated.

23.10 SANITISATION OF MATERIALS

This section addresses disinfection procedures using chemical agents during which fluids are applied to surfaces with the intention of' reducing the count of micro-organisms inside the controlled workspace of an isolator.

23.10.1 Introduction

Most isolator systems will require two different procedures:

- A procedure for treatment of the impervious internal surfaces of the isolator and external surfaces of the resident equipment.

- A second procedure for treating surfaces of transient components which will be present in the isolator for a particular procedure.

The cleaning down of equipment and related treatments can employ a wide range of agents. Components and other aids to production should usually be treated with alcohol-based preparations, which enable rapid evaporation of the solvent of such disinfectant agents and therefore facilitates a smooth, responsive work flow during production.

23.10.2 Methods for Treating Resident Surfaces

Transient material should be removed from the controlled workspace. Internal surfaces should be cleaned with a non-corrosive and low residue detergent. There should be no evidence of corrosion due to incompatibility with disinfection regimes.

23.10.3 Methods for Treating Transient Surfaces

The surfaces of components and aids to preparation (syringes etc.) should be treated by using rapid drying agents, such as aspectically filtered alcohol (70% w/v ethanol or isopropanol).

23.10.4 Disinfectants should not penetrate outer packaging and thus contaminate the contents.

23.11 GAS STERILISATION OF ISOLATOR SYSTEMS

23.11.1 Introduction

Alcohol-based solutions are routinely used to sanitise equipment and component surfaces during aseptic processing. The major disadvantage of this technique is that alcoholic agents process negligible activity against bacterial endospores. Control measures can minimise the incidence of spores on the surfaces of vials, syringe wraps etc; but their absence is not assured. A properly designed and validated gas treatment of isolator systems can reduce the probability of spores surviving and increase the sterility assurance of the product.

Gaseous agents may be introduced into the controlled workspace of the isolator system to sterilise the entire space, integral surfaces and transient or resident components inside. It reduces the numbers of viable micro-organisms to a predetermined and acceptable level.

23.11.2 Objectives of Gas Sterilization

Various gaseous agents can be used within suitably-designed isolators to achieve sterilisation of working and component surfaces, thereby significantly reducing the overall probability of sterility failure in the final product.

Note: This process does not guarantee product sterility, but merely eliminates one of the factors which can result in product contamination during aseptic processing.