Annex 1 : Manufacture of Sterile Products

Document map

Section Number	General overview
1. Scope	Includes additional areas (other than sterile products) where the general principles of the annex can be applied.
2. Principle	General principles as applied to the manufacture of sterile products.
3. Pharmaceutical Quality System (PQS)	Highlights the specific requirements of the PQS when applied to sterile products.
4. Premises	General guidance regarding the specific needs for premises design and also guidance on the qualification of premises including the use of Barrier Technology.
5. Equipment	General guidance on the design and operation of equipment.
6. Utilities	Guidance with regards to the special requirements of utilities such as water, gas and vacuum.
7. Personnel	Guidance on the requirements for specific training, knowledge and skills. Also gives guidance to the qualification of personnel.
8. Production and specific technologies	Discusses the approaches to be taken with regards to aseptic and terminal sterilization processes. Discusses approaches to sterilization of products, equipment and packaging components. Also discusses different technologies such as lyophilization and Form-Fill-Seal where specific requirements apply.
9. Viable and non-viable environmental and process monitoring	This section differs from guidance given in section 4 in that the guidance here applies to ongoing routine monitoring with regards to the design of systems and setting of action limits alert levels and reviewing trend data. The section also gives guidance on the requirements of Aseptic Process Simulation (APS).
10. Quality control (QC)	Gives guidance on some of the specific Quality Control requirements relating to sterile products.
11. Glossary	Explanation of specific terminology.

1 Scope

The manufacture of sterile products covers a wide range of sterile product types (active substance, sterile excipient, primary packaging material and finished dosage form), packed sizes (single unit to multiple units), processes (from highly automated systems to manual processes) and technologies (e.g. biotechnology, classical small molecule manufacturing and closed systems). This Annex provides general guidance that should be used for the manufacture of all sterile products using the principles of Quality Risk Management (QRM), to ensure that microbial, particulate and pyrogen contamination is prevented in the final product.

QRM applies to this document in its entirety and will not be referred to in specific paragraphs. Where specific limits or frequencies are written, these should be considered as a minimum requirement. They are stated due to regulatory historical experience of issues that have previously been identified and have impacted the safety of patients.

The intent of the Annex is to provide guidance for the manufacture of sterile products. However, some of the principles and guidance, such as contamination control strategy, design of premises, cleanroom classification, qualification, monitoring and personnel gowning, may be used to support the manufacture of other products that are not intended to be sterile such as certain liquids, creams, ointments and low bioburden biological intermediates but where the control and reduction of microbial, particulate and pyrogen contamination is considered important. Where a manufacturer elects to apply guidance herein to non-sterile products, the manufacturer should clearly document which principles have been applied and acknowledge that compliance with those principles should be demonstrated.

2 Principle

2.1 The manufacture of sterile products is subject to special requirements in order to minimize risks of microbial, particulate and pyrogen contamination. The following key areas should be considered:

i. Facility, equipment and process design should be optimized, qualified and validated according to the relevant sections of the Good Manufacturing Practices (GMP) guide. The use of appropriate technologies (e.g. Restricted Access Barriers Systems (RABS), isolators, robotic systems, rapid microbial testing and monitoring systems) should be considered to increase the protection of the product from potential extraneous sources of particulate and microbial contamination such as personnel, materials and the surrounding environment, and assist in the rapid detection of potential contaminants in the environment and product.

ii. Personnel should have adequate qualifications and experience, training and attitude with a specific focus on the principles involved in the protection of sterile product during the manufacturing, packaging and distribution processes.

iii. Processes and monitoring systems for sterile product manufacture should be designed, commissioned, qualified and monitored by personnel with appropriate process, engineering and microbiological knowledge.

2.2 Processes, equipment, facilities and manufacturing activities should be managed in accordance with QRM principles to provide a proactive means of identifying, scientifically evaluating and controlling potential risks to quality. Where alternative approaches are used, these should be supported by appropriate rationales and risk assessment and should meet the intent of this Annex.
QRM priorities should include good design of the facility, equipment and process in the first instance, then implementation of well-designed procedures, with monitoring systems as the final element that

demonstrate that the design and procedures have been correctly implemented and continue to perform in line with expectations. Exclusively monitoring or testing does not give assurance of sterility.

2.3 Quality Assurance is particularly important, and manufacture of sterile products must strictly follow carefully established and validated methods of manufacture and control. A Contamination Control Strategy (CCS) should be implemented across the facility in order to define all critical control points and assess the effectiveness of all the controls (design, procedural, technical and organisational) and monitoring measures employed to manage risks associated with contamination. The CCS should be actively updated and should drive continuous improvement of the manufacturing and control methods.

2.4 Contamination control and steps taken to minimize the risk of contamination from microbial and particulate sources are a series of successively linked events and measures. These are typically assessed, controlled and monitored individually but their collective effectiveness should be considered altogether.

2.5 The development of the CCS requires thorough technical and process knowledge. Potential sources of contamination are attributable to microbial and cellular debris (e.g. pyrogen, endotoxins) as well as particulate matter (e.g. glass and other visible and sub-visible particulates).
Elements to be considered within a documented CCS should include (but are not limited to):

i. Design of both the plant and processes.

ii. Premises and equipment.

iv. Personnel.

v. Utilities.

vi. Raw material controls – including in-process controls.

vii. Product containers and closures.

viii. Vendor approval – such as key component suppliers, sterilization of components and single use systems (SUS), and services.

ix. For outsourced services, such as sterilization, sufficient evidence should be provided to the contract giver to ensure the process is operating correctly.

x. Process risk assessment.

xi. Process validation.

xii. Preventative maintenance – maintaining equipment, utilities and premises (planned and unplanned maintenance) to a standard that will not add significant risk of contamination.

xiii. Cleaning and disinfection.

xiv. Monitoring systems - including an assessment of the feasibility of the introduction of scientifically sound, modern methods that optimize the detection of environmental contamination.

xv. Prevention – trending, investigation, corrective and preventive actions (CAPA), root cause determination and the need for more comprehensive investigational tools.

xvi. Continuous improvement based on information derived from the above.

2.6 The CCS should consider all aspects of contamination control and its life cycle with ongoing and periodic review resulting in updates within the quality system as appropriate.

2.7 The manufacturer should take all steps and precautions necessary to assure the sterility of the products manufactured within its facilities. Sole reliance for sterility or other quality aspects should not be placed on any terminal process or finished product test.

3 Pharmaceutical Quality System (PQS)

3.1 The manufacture of sterile products is a complex activity that requires specific controls and measures to ensure the quality of products manufactured. Accordingly, the manufacturer's PQS should encompass and address the specific requirements of sterile product manufacture and ensure that all activities are effectively controlled so that microbial, particulate and pyrogen contamination is minimized in sterile products. In addition to the PQS requirements detailed in Chapter 1 of the GMPs, the PQS for sterile product manufacture should also ensure that:

i. An effective risk management system is integrated into all areas of the product life cycle with the aim to minimize microbial contamination and to ensure the quality of sterile products manufactured.

ii. The manufacturer has sufficient knowledge and expertise in relation to the products manufactured and the equipment, engineering and manufacturing methods employed that have an impact on product quality.

iii. Root cause analysis of procedural, process or equipment failure is performed in such a way that the risk to product is correctly understood and suitable corrective and preventative actions (CAPA) are implemented.

iv. Risk management is applied in the development and maintenance of the CCS, to identify, assess, reduce/eliminate (where applicable) and control contamination risks. Risk management should be documented and should include the rationale for decisions taken in relation to risk reduction and acceptance of residual risk.

v. The risk management outcome should be reviewed regularly as part of on-going quality management, during change control and during the periodic product quality review.

vi. Processes associated with the finishing and transport of sterile products should not compromise the sterile product. Aspects that should be considered include: container integrity, risks of contamination and avoidance of degradation by ensuring that products are stored and maintained in accordance with the registered storage conditions.

vii. Persons responsible for the quality release of sterile products have appropriate access to manufacturing and quality information and possess adequate knowledge and experience in the manufacture of sterile products and their critical quality attributes. This is in order to allow such persons to ascertain that the sterile products have been manufactured in accordance with the registered specifications and are of the required quality.

3.2 All non-conformities, such as sterility test failures, environmental monitoring excursions or deviations from established procedures should be investigated. The investigation should determine the potential impact upon process and product quality and whether any other processes or batches are potentially impacted. The reason for including or excluding a product or batch from the scope of the investigation should be clearly justified and recorded.

4 Premises

4.1 The manufacture of sterile products should be carried out in appropriate cleanrooms, entry to which should be through changing rooms that act as airlocks for personnel and airlocks for equipment and materials. Cleanrooms should be maintained to an appropriate cleanliness standard and supplied with air which has passed through filters of an appropriate efficiency. Controls and monitoring should be scientifically justified and capable of evaluating the state of environmental conditions for cleanrooms, airlocks and pass-throughs used for material and equipment transfer.

4.2 The various operations of component preparation, product preparation and filling should be carried out with appropriate technical and operational separation measures within the cleanroom or facility to prevent mix up and contamination.

4.3 Restricted Access Barrier Systems (RABS) and isolators are beneficial in assuring the required conditions and minimizing the microbial contamination associated with direct human interventions in the critical zone. Their use should be considered in the CCS. Any alternative approaches to the use of RABS or isolators should be justified.

4.4 For the manufacture of sterile products there are four grades of cleanroom.

Grade A zone: The critical zone for high risk operations or for making aseptic connections by ensuring protection by first air (e.g. aseptic processing line, filling zone, stopper bowl, open ampoules and vials). Normally, such conditions are provided by a localised airflow protection, such as unidirectional airflow work stations, RABS or isolators. The maintenance of unidirectional airflow should be demonstrated and qualified across the whole of the Grade A zone. Direct intervention (e.g. without the protection of barrier and glove port technology) into the Grade A zone by operators should be minimized by premises, equipment, process and procedural design.

Grade B area: For aseptic preparation and filling, this is the background cleanroom for the Grade A zone (where it is not an isolator). When transfer holes are used to transfer filled, closed products to an adjacent cleanrooms of a lower grade, airflow visualization studies should demonstrate that air does not ingress from the lower grade cleanrooms to the Grade B. Pressure differentials should be continuously monitored. Cleanrooms of lower grade than Grade B can be considered where isolator technology is used (refer to paragraph 4.22).

Grade C and D area: These are cleanrooms used for carrying out less critical stages in the manufacture of aseptically filled sterile products but can be used for the preparation /filling of terminally sterilized products. (See section 8 for the specific details on terminal sterilization activities).

4.5 In cleanrooms, all exposed surfaces should be smooth, impervious and unbroken in order to minimize the shedding or accumulation of particulates or micro-organisms and to permit the repeated application of cleaning, disinfectant and sporicidal agents where used.

4.6 To reduce accumulation of dust and to facilitate cleaning there should be no recesses that are difficult to clean effectively therefore projecting ledges, shelves, cupboards and equipment should be kept to a minimum. Doors should be designed to avoid recesses that cannot be cleaned.

4.7 Materials used in cleanrooms should be selected to minimize generation of particles.

4.8 Ceilings should be designed and sealed to prevent contamination from the space above them.

4.9 Sinks and drains are prohibited in Grade A zone and Grade B area. In other cleanrooms, air breaks should be fitted between the machine or sink and the drains. Floor drains in lower grade cleanrooms should be fitted with traps or water seals designed to prevent back flow and should be regularly cleaned, disinfected and maintained.

4.10 The transfer of equipment and materials into and out of the cleanrooms and critical zones is one of the greatest potential sources of contamination. Any activities with the potential to compromise the cleanliness of cleanrooms or the critical zone should be assessed and if they cannot be eliminated, appropriate controls should be implemented.

4.11 The transfer of materials, equipment, and components into an aseptic processing area should be carried out via a unidirectional process. Where possible, items should be sterilized and passed into the area through double-ended sterilizers (e.g. through a double-door autoclave or depyrogenation oven/tunnel) sealed into the wall. Where sterilization on transfer of the items is not possible, a procedure which achieves the same objective of not introducing contaminant should be validated and implemented, (e.g. using an effective transfer disinfection, rapid transfer systems for isolators or, for gaseous or liquid materials, a bacteria-retentive filter).

4.12 Airlocks should be designed and used to provide physical separation and to minimize microbial and particulate contamination of the different areas, and should be present for material and personnel moving between different grades. Wherever possible, airlocks used for personnel movement should be separated from those used for material movement. Where this is not practical, time-based separation of movement (personnel /material) by procedure should be considered. Airlocks should be flushed effectively with filtered air to ensure that the grade of the cleanroom is maintained. The final stage of the airlock should, in the “at rest” state, be of the same cleanliness grade (viable and non-viable) as the cleanroom into which it leads. The use of separate changing rooms for entering and leaving Grade B cleanrooms is desirable. Where this is not practical, time-based separation of activities (ingress/egress) by procedure should be considered. Where the CCS indicates that the risk of cross-contamination is high, separate changing rooms for entering and leaving production areas should be considered. Airlocks should be designed as follow:

i. Personnel airlocks: Areas of increasing cleanliness used for entry of personnel (e.g. from Grade D to Grade C to Grade B). In general hand washing facilities should be provided only in the first stage of the changing room and not be present in changing rooms directly accessing Grade B cleanrooms.

ii. Material airlocks: used for materials and equipment transfer.

   - Only materials and equipment that have been included on an approved list, developed during validation of the transfer process, should be allowed to be transferred into the Grade A zone or Grade B cleanroom via an airlock or pass-through hatch. Equipment and materials (intended for use in the Grade A zone) should be protected when transiting through the Grade B cleanroom. Any unapproved items that require transfer should be pre-approved as an exception. Appropriate risk assessment and mitigation measures should be applied and recorded as per the manufacturer's CCS and should include a specific disinfection and monitoring programme approved by quality assurance.

   - Pass-through hatches should be designed to protect the higher grade environment, for example by effective flushing with an active filtered air supply.

   - The movement of material or equipment from lower grade or unclassified area to higher grade clean areas should be subject to cleaning and disinfection commensurate with the risk and in line with the CCS.

4.13 Both sets of doors for pass-throughs and airlocks (for material and personnel) should not be opened simultaneously. For airlocks leading to a Grade A zone and Grade B areas, an interlocking system should be used. For airlocks leading to Grade C and D cleanrooms, a visual and/or audible warning system should be operated as a minimum. Where required to maintain zone segregation, a time delay between the closing and opening of interlocked doors should be established.

4.14 Cleanrooms should be supplied with a filtered air supply that maintains a positive pressure and/or an airflow relative to the background environment of a lower grade under all operational conditions and should flush the area effectively. Adjacent rooms of different grades should have pressure differentials of a minimum of 10 pascals (guidance value). Particular attention should be paid to the protection of the critical zone. The recommendations regarding air supplies and pressures may need to be modified where it is necessary to contain certain materials (e.g. pathogenic, highly toxic or radioactive products or live viral or bacterial materials). The modification may include positively or negatively pressurized airlocks that prevent the hazardous material from contaminating surrounding areas. Decontamination of facilities (e.g. the cleanrooms and the heating, ventilation, and air conditioning (HVAC) systems) and the treatment of air leaving a clean area, may be necessary for some operations. Where containment requires air to flow into a critical zone, the source of the air should be from an area of the same grade.

4.15 Airflow patterns within cleanrooms and zones should be visualised to demonstrate that there is no ingress from lower grade to higher grade areas and that air does not travel from less clean areas (such as the floor) or over operators or equipment that may transfer contaminant to the higher grade areas. Where air movement is shown to be a risk to the clean area or critical zone, corrective actions, such as design improvement, should be implemented. Airflow pattern studies should be performed both at rest and in operation (e.g. simulating operator interventions). Video recordings of the airflow patterns should be retained. The outcome of the air visualisation studies should be considered when establishing the facility's environmental monitoring program.

4.16 Indicators of pressure differences should be fitted between cleanrooms and/or isolators. Set-points and the criticality of pressure differentials should be documented within the CCS. Pressure differentials identified as critical should be continuously monitored and recorded. A warning system should be in place to instantly indicate and warn operators of any failure in the air supply or reduction of pressure differentials (below set limits for those identified as critical). The warning signal should not be overridden without assessment and a procedure should be available to outline the steps to be taken when a warning signal is given. Where alarm delays are set, these should be assessed and justified within the CCS. Other pressure differentials should be monitored and recorded at regular intervals.

4.17 Facilities should be designed to permit observation of production activities from outside the Grade A zone and Grade B area (e.g. through the provision of windows or remote cameras with a full view of the area and processes to allow observation and supervision without entry). This requirement should be considered when designing new facilities or during refurbishment of existing facilities.

Barrier Technologies

4.18 Isolator or RABS technologies, and the associated processes, should be designed to provide protection of the Grade A environment. The entry of materials during processing (and after decontamination) should be minimized and preferably supported by rapid transfer technologies or transfer isolators.

4.19 The design of the RABS or isolator should take into account all critical factors associated with these technologies including the quality of the air inside and the background environment, the materials and component transfer, the decontamination and/or sterilization processes, the risk factors associated with the manufacturing operations and the operations conducted within the critical zone.

4.20 The critical zone of the RABS or open isolator used for aseptic processes should meet Grade A requirements with unidirectional airflow. In closed isolator systems where airflow may not be unidirectional, it should provide Grade A conditions and be demonstrated to provide adequate protection for exposed products during processing. The design of the RABS and open isolators should ensure a positive airflow from the critical zones to the supporting background environment; (unless containment is required in which case localized air extraction is required to prevent contamination transfer to the surrounding room). Negative pressure isolators should only be used when containment of the product is considered essential and risk control measures are applied to ensure the critical zone is not compromised.

4.21 For RABS used for aseptic processing, the background environment should meet at least Grade B. The background environment for open isolators should meet Grade C or D, based on a risk assessment. Airflow studies should be performed to demonstrate the absence of air ingress during interventions, such as door openings.

4.22 The background environment of a closed isolator should correspond to a minimum of Grade D. The disinfection/decontamination programme should be included as a key consideration when performing the risk assessment for the CCS of an isolator. Where additional process risks are identified, a higher grade of background should be considered. The decision as to the supporting background environment should be documented in the CCS.

4.23 The materials used for glove systems (for both RABS and isolators), as well as other parts of an isolator, should be demonstrated to have good mechanical and chemical resistance. Integrity testing of the barrier systems, and leak testing of the glove system and the isolator should be performed using a methodology demonstrated to be suitable for the task and criticality. The testing should be performed at defined periods, at a minimum at the beginning and end of each batch, and should include a visual inspection following any intervention that may affect the integrity of the system. For single unit batch sizes, integrity may be verified based on other criteria, such as the beginning and end of each manufacturing session. RABS gloves used in Grade A zone should be sterilized before installation and sterilized (or effectively decontaminated by a validated method which achieves the same objective) prior to each manufacturing campaign. The frequency of glove replacement should be defined within the CCS.

4.24 For RABS and isolator systems, decontamination methods should be validated and controlled within defined cycle parameters. The cleaning process prior to the disinfection step is essential; any residues that remain may inhibit the effectiveness of the decontamination process:

i. For isolators, the decontamination process should be automated and should include a sporicidal agent in a suitable form (e.g. gaseous, aerosolized or vaporized form) to ensure thorough microbial decontamination of its interior. Decontamination methods (cleaning and sporicidal disinfection) should render the interior surfaces and critical zone of the isolator free of viable microorganisms.

ii. For RABS systems, the disinfection should include the routine application of a sporicidal agent using a method that has been validated and demonstrated to robustly disinfect the interior and ensure a suitable environment for aseptic processing.

Evidence should also be available to demonstrate that the agent used does not have adverse impact on the product produced within the RABS or isolator. The holding time before use of these systems should be validated.

Cleanroom and clean air equipment qualification

4.25 Cleanrooms and clean air equipment such as unidirectional airflow units (UDAFs), RABS and isolators, used for the manufacture of sterile products, should be qualified and classified according to the required characteristics of the environment. Each manufacturing operation requires an appropriate environmental cleanliness level in the operational state in order to minimize the risk of particulate or microbial contamination of the product or materials being handled.

4.26 Cleanrooms and clean air equipment should be qualified using methodology in accordance with the requirements of Annex 15. Cleanroom qualification (including classification) should be clearly differentiated from operational environmental monitoring.

4.27 Cleanroom Qualification is the overall process of assessing the level of compliance of a classified cleanroom or clean air equipment with its intended use. As part of the qualification requirements of Annex 15, the qualification of cleanrooms and clean air equipment should include (where relevant to the design/operation of the installation):

i. Installed filter leakage and integrity testing.

ii. Airflow measurement - Volume and velocity.

iii. Air pressure difference measurement.

iv. Airflow direction and visualisation.

v. Microbial airborne and surface contamination.

vi. Temperature measurement.

vii. Relative humidity measurement.

viii. Recovery testing.

ix. Containment leak testing.

4.28 Cleanroom classification is part of a cleanroom qualification and is a method of assessing the level of air cleanliness against a specification for a cleanroom or clean air equipment by measuring the non-viable airborne particulate concentration. Reference for the classification of the cleanrooms and clean air equipment can be found in the ISO 14644 series of standards.

4.29 For cleanroom classification, the airborne particulates equal to or greater than 0.5 and 5 µm should be measured. For Grade A zone and Grade B at rest, classification should include measurement of particles equal to or greater than 0.5 µm; however, measurement using a second, larger particle size, e.g. 1 µm in accordance with ISO 14644 may be considered. This measurement should be performed both at rest and in operation. The maximum permitted airborne particulate concentration for each grade is given in Table 1.

Table 1: Maximum permitted airborne particulate concentration during classification

Grade	Maximum limits for particulates ≥ 0.5 μm/m³		Maximum limits for particulates ≥ 5 μm/m³	
	at rest	in operation	at rest	in operation
A	3 520	3 520	Not applicable	Not applicable
B	3 520	352 000	Not applicable	2 900
C	352 000	3 520 000	2 900	29 000
D	3 520 000	Not defined[a]	29 000	Not defined[a]

[a] For Grade D, in operation limits are not defined. The company should establish in operation limits based on a risk assessment and historical data where applicable.

4.30 For classification of the cleanroom, the minimum number of sampling locations and their positioning can be found in ISO 14644 Part 1. In addition, for the aseptic processing room and the background environment (Grade A zone and Grade B area, respectively), sample locations should also consider all critical processing zones such as the point of fill and stopper bowls. Critical processing locations should be based on a documented risk assessment and knowledge of the process and operations to be performed in the area.

4.31 Clean room classification should be carried out in the “at rest” and “in operation” states.

i. The definition of “at rest” state is the condition whereby the installation of all the utilities is complete including any functioning HVAC, with the main manufacturing equipment installed as specified and standing by for operation, without personnel in the room.

ii. The definition of “in operation” state is the condition where the installation of the cleanroom is complete, the HVAC system fully operational, equipment installed and functioning in the manufacturer’s defined operating mode with the maximum number of personnel present performing or simulating routine operational work. In operation classification may be performed during simulated operations or during aseptic process simulations (where worst case simulation is required).

iii. The particulate limits given in Table 1 above for the “at rest” state should be achieved after a “clean up” period on completion of operations. The "clean up" period should be determined during the classification of the rooms (guidance value of 15 to 20 minutes).

4.32 The speed of air supplied by unidirectional airflow systems should be clearly justified in the qualification protocol including the location for air speed measurement. Air speed should be designed, measured and maintained to ensure that appropriate unidirectional air movement provides protection of the product and open components at the working height (e.g. where high risk operations and product and/or components are exposed). Unidirectional airflow systems should provide a homogeneous air speed in a range of 0.36 – 0.54 m/s (guidance value) at the working position, unless otherwise scientifically justified in the CCS. Airflow visualization studies should correlate with the air speed measurement.

4.33 The microbial concentration of the cleanrooms should be determined as part of the cleanroom qualification. The number of sampling locations should be based on a documented risk assessment, including the results of the classification, air visualization studies and knowledge of the process and operations to be performed in the area. The maximum limits for microbial contamination during qualification for each grade are given in Table 2. Qualification should include both at rest and in operation states.

Table 2: **Limits for microbial contamination during qualification**

Grade	Air sample cfu/m^3	Settle plates (diameter 90 mm) cfu/4 hours [a]	Contact plates (diameter 55 mm) cfu/plate
A[b]	No growth[b]		
B	10	5	5
C	100	50	25
D	200	100	50

(a) Settle plates should be exposed for the duration of operations and changed as required after 4 hours. Exposure time should be based on recovery studies and should not allow desiccation of the media used.

(b) It should be noted that for Grade A, the expected result should be no growth.

Note 1: All methods indicated for a specific Grade in the table should be used for qualifying the area of that specific Grade. If one of the methods is not used, or alternative methods are used, the approach taken should be appropriately justified.

Note 2: Limits are applied using cfu throughout the document. If different or new technologies are used that present results in a manner different from cfu, the manufacturer should scientifically justify the limits applied and where possible correlate them to cfu.

Note 3: For qualification of personnel gowning, the limits given for contact plates and glove prints in Table 7 should apply.

Note 4: Sampling methods should not pose a risk of contamination to the manufacturing operations.

4.34 The requalification of cleanrooms and clean air equipment should be carried out periodically following defined procedures. The requirement for requalification of cleanroom areas is as follows:

Table 3: Minimum test requirements for the requalification of cleanrooms

Grade	Determination of the concentration of airborne viable and non-viable particles	Integrity Test of Terminal Filters	Airflow volume measurement	Verification of air pressure difference between rooms	Air Velocity test
A	Yes	Yes	Yes	Yes	Yes
B	Yes	Yes	Yes	Yes	*
C	Yes	Yes	Yes	Yes	*
D	Yes	Yes	Yes	Yes	*

* performed according to a risk assessment documented as part of the CCS. However, required for filling zones (e.g. when filling terminally sterilised products) and background to Grade A RABS.

For Grade A & B areas, the maximum time interval for requalification is 6 months.
For Grade C & D areas, the maximum time interval for requalification is 12 months.
Appropriate requalification consisting of at least the above tests should also be carried out following completion of remedial action implemented to rectify an out-of-compliance equipment or facility condition or after changes to equipment, facility or processes. The significance of a change should be determined through the change management process. Examples of changes to be considered include but are not limited to the following:

i. Change in the operational use of the cleanroom, or of the operational setting parameters of the HVAC system.

ii. Interruption of air movement which affects the operation of the installation.

iii. Special maintenance which affects the operation of the installation (e.g. change of final filters).

4.35 Other characteristics, such as temperature and relative humidity, should be controlled within ranges that align with product/processing requirements and support maintenance of defined cleanliness standards (e.g. Grade A or B).

Disinfection

4.36 The disinfection of cleanrooms is particularly important. They should be cleaned and disinfected thoroughly in accordance with a written programme. For disinfection to be effective, prior cleaning to remove surface contamination should be performed. More than one type of disinfecting agent should be employed to ensure that where they have different modes of action and their combined usage is effective against all bacteria and fungi. Disinfection should include the periodic use of a sporicidal agent. Monitoring should be undertaken regularly in order to assess the effectiveness of the disinfection program and to detect changes in types of microbial flora (e.g. organisms resistant to the disinfection regime currently in use). Cleaning programs should effectively remove disinfectant residues.

4.37 The disinfection process should be validated. Validation studies should demonstrate the suitability and effectiveness of disinfectants in the specific manner in which they are used and should support the in-use expiry periods of prepared solutions.

4.38 Disinfectants and detergents used in Grade A zone and Grade B areas should be sterile prior to use (disinfectants used in Grade C and D may also be required to be sterile). Where the disinfectants and detergents are made up by the sterile product manufacturer, they should be monitored for microbial contamination. Dilutions should be kept in previously cleaned containers and should only be stored for defined periods. If the disinfectants and detergents are supplied “ready-made” then results from certificates of analysis or conformance can be accepted subject to successful completion of the appropriate vendor qualification.

4.39 Fumigation or vapour disinfection (e.g. Vapour-phased Hydrogen Peroxide) of cleanrooms and associated surfaces may be useful for reducing microbial contamination in inaccessible places.

5 Equipment

5.1 A written, detailed description of the equipment design should be available (including process and instrumentation diagrams as appropriate). This should form part of the initial qualification package and be kept up to date as part of the ongoing review of the CCS.

5.2 Equipment monitoring requirements should be defined in “user requirements specifications” and during early stages of development, and confirmed during qualification. Process and equipment alarm events should be reviewed and approved and evaluated for trends. The frequency at which alarms are assessed should be based on their criticality (with critical alarms reviewed immediately).

5.3 As far as practicable, equipment, fittings and services should be designed and installed so that operations, maintenance, and repairs can be performed outside the cleanroom. If maintenance has to be performed in the cleanroom, and the required standards of cleanliness and/or asepsis cannot be maintained, then precautions such as restricting access to the work area to specified personnel, generation of clearly defined work protocols and maintenance procedures should be considered. Cleaning, additional disinfection and additional environmental monitoring should also be considered. If sterilization of equipment is required, it should be carried out, wherever possible, after complete reassembly.

5.4 The cleaning process should be validated to:

i. Remove any residue or debris that would detrimentally impact the effectiveness of the disinfecting agent used.
ii. Minimize chemical, microbial and particulate contamination of the product during the process and prior to disinfection.

5.5 Direct and indirect contact parts should be sterilized. Direct contact parts are those that the product passes through, such as filling needles or pumps. Indirect product contact parts are equipment parts that come into contact with sterilized critical items and components.

5.6 All equipment such as sterilizers, air handling systems (including air filtration) and water systems should be subject to qualification, monitoring and planned maintenance. Upon completion of maintenance, their return to use should be approved.

5.7 Where unplanned maintenance of equipment critical to the sterility of the product is to be carried out, an assessment of the potential impact to the sterility of the product should be performed and recorded.

5.8 A conveyor belt should not pass through a partition between a Grade A or B area and a processing area of lower air cleanliness, unless the belt itself is continually sterilized (e.g. in a sterilizing tunnel).

5.9 Particle counters, including sampling tubing, should be qualified. The tubing length should be no greater than 1 meter with a minimum number of bends and bend radius should be greater than 15 cm. Portable particle counters with a short length of sample tubing should be used for classification purpose. Isokinetic sampling heads should be used in unidirectional airflow systems and should be positioned as close as possible to sample air representative of the critical location.

6 Utilities

6.1 The nature and extent of controls applied to utility systems should be commensurate with the risk to product quality associated with the utility. The impact should be determined via a risk assessment documented as part of the CCS.

6.2 In general higher risk utilities are those that:

i. Directly contact product e.g. water for washing and rinsing, gases and steam for sterilization.

ii. Contact materials that will ultimately become part of the product.

iii. Contact surfaces that come into contact with the product.

iv. Otherwise directly impact the product.

6.3 Utilities should be designed, installed, operated, maintained and monitored in a manner to ensure that the utility functions as expected.

6.4 Results for critical parameters and critical quality attributes of high risk utilities should be subject to regular trend analysis to ensure that system capabilities remain appropriate.

6.5 Records of utility installation should be maintained throughout the system's life-cycle. Such records should include current drawings and schematic diagrams, construction material lists and specifications. Typically, important information includes attributes such as:

i. Pipeline flow direction, slopes, diameter and length.

ii. Tank and vessel details.

iii. Valves, filters, drains, sampling and user points.

6.6 Pipes, ducts and other utilities should not be present in cleanrooms. If unavoidable, then they should be installed so that they do not create recesses, unsealed openings and surfaces which are difficult to clean. Installation should allow cleaning and disinfection of outer surface of the pipes.

Water systems

6.7 Water treatment plant and distribution systems should be designed, constructed and maintained to minimize the risk of particulates, microbial contamination/proliferation and pyrogens (e.g. sloping of piping to provide complete drainage and the avoidance of dead legs), and prevent the formation of biofilms to ensure a reliable source of water of an appropriate quality. Where filters are included in the system, special attention should be given to the monitoring and maintenance of these filters. Water produced should comply with the current monograph of the relevant Pharmacopeia.

6.8 Water systems should be qualified to maintain the appropriate levels of physical, chemical and microbial control, taking seasonal variation into account.

6.9 Water flow should remain turbulent through the pipes to minimize the risk of microbial adhesion, and subsequent biofilm formation.

6.10 Water for injections (WFI) should be produced from water meeting specifications that have been defined during the qualification process, stored and distributed in a manner which minimizes the risk of microbial growth (for example by constant circulation at a temperature above 70°C). Where the WFI is produced by methods other than distillation, further techniques such as nanofiltration and ultra-filtration as well as electrodeionization (EDI) should be considered in conjunction with reverse osmosis (RO) membranes.

6.11 Where WFI storage tanks are equipped with hydrophobic bacteria retentive vent filters, the filters should be sterilized and the integrity of the filter tested before installation and after removal following use.

6.12 To minimize the risk of biofilm formation, sterilization or disinfection or regeneration of water systems should be carried out according to a predetermined schedule and when microbial counts exceed action limits. Disinfection of a water system with chemicals should be followed by a validated rinsing/flushing procedure. Water should be tested after disinfection/regeneration. The results should be approved before the water system is returned to use.

6.13 Regular ongoing chemical and microbial monitoring of water systems should be performed. Alert levels should be based on the qualification or a review of ongoing monitoring data that will identify an adverse trend in system performance. Sampling programs should reflect the requirements of the CCS and include:

i. All points of use, at a specified interval, to ensure that representative water samples are obtained for analysis on a regular basis.

ii. Potential worst case sampling locations.

iii. A sample from the point at the end of the distribution loop each day that the water is used.

6.14 Breaches of alert levels should be documented and reviewed, and include investigation of system trends to determine whether the breach is a single (isolated) event or if results are indicative of loss of control or system deterioration. Each breach of action limits should be investigated to determine the root cause of the issue and any impact on the quality of products and manufacturing processes as a result of the potential use of the water.

6.15 WFI systems should include continuous monitoring systems such as Total Organic Carbon (TOC) and conductivity, (unless justified otherwise) as these may give a better indication of overall system performance than discrete sampling. Sensor locations should be based on risk and the outcome of qualification.

Steam used as a direct sterilizing agent

6.16 Feed water to a pure steam (clean steam) generator should be appropriately purified. Pure steam generators should be designed, qualified and operated in a manner to ensure that the quality of steam produced meets defined chemical and endotoxin levels.

6.17 Steam used as a direct sterilizing agent should be of suitable quality and should not contain additives at a level which could cause contamination of product or equipment. For a pure steam generator supplying pure steam used for the direct sterilization of materials or product-contact surfaces (e.g. porous hard-good autoclave loads), steam condensate should meet the current monograph for WFI of the relevant Pharmacopeia. A suitable sampling schedule should be in place to ensure that representative pure steam samples are obtained for analysis on a regular basis. Other aspects of the quality of pure steam used for sterilization should be assessed periodically against validated parameters. These parameters should include the following: non-condensable gases, dryness value (dryness fraction) and superheat.

Gases and vacuum systems

6.18 Gases that come in direct contact with the product/primary container surfaces should be of appropriate chemical, particulate and microbial quality. All relevant parameters, including oil and water content, should be specified, taking into account the use and type of the gas, the design of the gas generation system and, where applicable, comply with the appropriate Pharmacopoeia monographs.

6.19 Gases used in aseptic processes should be filtered through a sterilizing filter (with a nominal pore size of a maximum of 0.22 µm) at the point of use. Where the filter is used on a batch basis (e.g. for filtration of gas used for overlay of aseptically filled products) or as product vessel vent filter, then the filter should be integrity tested and the results included as part of the batch certification process. Any transfer pipework or tubing that is located after the final sterilizing filter should be sterilized. When gases are used in the process, microbial monitoring of the gas should be performed periodically at the point of use.

6.20 Where backflow from vacuum or pressure systems poses a potential risk to the product, there should be mechanism(s) to prevent backflow when the vacuum or pressure system is shut off.

Heating and cooling and hydraulic systems

6.21 Major items of equipment associated with hydraulic, heating and cooling systems, e.g. such as those associated with Blow-Fill-Seal equipment should, where possible, be located outside the filling room. Where they are located inside the filling room there should be appropriate controls to contain any spillage and/or cross contamination associated with the hydraulic system fluids. Where possible, the system should be at a lower pressure than the processed fluid.

6.22 Any leaks from these systems that would present a risk to the product should be detectable (i.e. an indication system for leakage).

6.23 For both vacuum and cooling systems there should be periodic cleaning/disinfection as determined in the CCS.

7 Personnel

7.1 The manufacturer should ensure that there are sufficient appropriate personnel, suitably qualified, trained and experienced in the manufacture and testing of sterile products, and any of the specific manufacturing technologies used in the site's manufacturing operations, to ensure compliance with GMP applicable to the manufacture and handling of sterile products.

7.2 Only the minimum number of personnel required should be present in cleanrooms. The maximum number of operators in cleanrooms should be determined, documented and validated during activities such as initial qualification and aseptic process simulations, so as not to compromise sterility assurance. This is particularly important during aseptic processing.

7.3 Non-essential processes such as product inspection and in process testing should be conducted outside the clean areas wherever possible.

7.4 All personnel including those performing cleaning, maintenance, monitoring and those that access cleanrooms should receive regular training, gowning qualification and assessment in disciplines relevant to the correct manufacture of sterile products. This training should include the basic elements of microbiology, hygiene, with a specific focus on cleanroom practices, contamination control, aseptic techniques and the protection of sterile products (for those operators entering the Grade B cleanrooms and/or intervening into the Grade A zone) and the potential safety implications to the patient if product is not sterile. The level of training should based on the criticality of the function and area in which the personnel are working.

7.5 The personnel working in a Grade A zone and Grade B areas should be trained for aseptic gowning and aseptic practices. Compliance with aseptic gowning procedures should be assessed and confirmed, periodically reassessed at least annually and should involve both visual and microbial assessment (using monitoring locations such as hands, arms, chest and forehead. Refer to paragraph 9.30 for the expected limits). The unsupervised access to Grade A zone and Grade B areas where aseptic operations are or will be conducted should be restricted to appropriately qualified personnel, who have passed the gowning assessment and have participated in a successful aseptic process simulation (APS).

7.6 Unqualified personnel (e.g. building and maintenance contractors and regulatory inspectors) should not enter Grade B cleanrooms or Grade A zones in operation. If needed in exceptional cases, manufacturers should establish written procedures outlining the process by which unqualified personnel are brought into the Grade B and A areas. Access by these persons should be assessed and recorded in accordance with the PQS. An authorized person from the manufacturer should supervise the unqualified personnel during their activities and should assess the impact of these activities on the cleanliness of the area.

7.7 There should be systems in place for disqualification of personnel from entry into cleanrooms based on aspects including ongoing assessment and/or identification of an adverse trend from the personnel monitoring program and/or after participation in a failed APS. Once disqualified, retraining and requalification should be completed before permitting the operator to have any further involvement in aseptic practices. For operators entering Grade B cleanrooms or performing intervention into Grade A zone, this requalification should include consideration of participation in a successful APS.

7.8 High standards of personal hygiene and cleanliness are essential to prevent excessive shedding or increased risk of introduction of microbial contamination. Personnel involved in the manufacture of sterile products should be instructed to report any specific health conditions or ailments which may cause the shedding of abnormal numbers or types of contaminants and therefore preclude cleanroom access. Health conditions and actions to be taken with regard to personnel who could be introducing an undue microbial hazard should be provided by the designated competent person and described in procedures.

7.9 Staff who have been engaged in the processing of human or animal tissue materials or of cultures of micro-organisms, other than those used in the current manufacturing process, or any activities that may have a negative impact to quality (e.g. microbial contamination), should not enter clean areas unless clearly defined and effective decontamination and entry procedures have been followed.

7.10 Wristwatches, make-up, jewellery, other personal items such as mobile phones and any other non-essential items should not be allowed in clean areas. Electronic devices used in cleanrooms, e.g. mobile phones and tablets, that are supplied by the company solely for use in the cleanrooms, may be acceptable if suitably designed to permit cleaning and disinfection commensurate with the Grade in which they are used. The use and disinfection of such equipment should be included in the CCS.

7.11 Cleanroom gowning and hand washing should follow a written procedure designed to minimize contamination of cleanroom clothing and/or the transfer of contaminants to the clean areas.

7.12 The clothing and its quality should be appropriate for the process and the grade of the working area. It should be worn in such a way as to protect the product from contamination. When the type of clothing chosen needs to provide the operator protection from the product, it should not compromise the protection of the product from contamination. Garments should be visually checked for cleanliness and integrity immediately prior to gowning and prior to entry to the cleanroom. Gown integrity should also be checked upon exit. For sterilized or effectively decontaminated garments and eye coverings, particular attention should be taken to ensure they have been processed, are within their specified hold time and that the packaging is visually inspected to ensure it is integral before use. Reusable garments (including eye coverings) should be replaced if damage is identified or at a set frequency that is determined during qualification studies. . Damage to garments may not be identified by visual inspection alone, so the qualification should consider any necessary garment testing requirements.

7.13 Clothing should be chosen to prevent shedding due to operators moving excessively (when cold) or sweating (when hot).

7.14 The description of clothing required for each grade is given below:

i. Grade A / B: Dedicated garments to be worn under a sterilized suit. Sterile headgear should enclose all hair (including facial hair) and where separate from the rest of the gown, it should be tucked into the neck of the sterile suit. A sterile face mask and sterile eye coverings (e.g. goggles) should be worn to cover and enclose all facial skin and prevent the shedding of droplets and particulates. Appropriate sterilized, non-powdered, rubber or plastic gloves and sterilized footwear (such as overboots) should be worn. Trouser-legs should be tucked inside the footwear and garment sleeves into the gloves. The protective clothing should minimize shedding of fibres or particulate matter and retain particulates shed by the body. Garments should be packed and folded in such a way as to allow operators to gown without contacting the outer surface of the garment.

ii. Grade C: Hair, beards and moustaches should be covered. A single or two-piece trouser suit gathered at the wrists and with high neck and appropriately disinfected shoes or overshoes should be worn. They should minimize the shedding of fibres and particulate matter.

iii. Grade D: Hair, beards and moustaches should be covered. A general protective suit and appropriately disinfected shoes or overshoes should be worn. Appropriate measures should be taken to avoid any ingress of contaminants from outside the clean area.

iv. Gloves should be worn in Grade C and D areas when performing activities considered to be a contamination risk as defined by the CCS.

7.15 Outdoor clothing (other than personal underwear) should not be brought into changing rooms leading directly to Grade B and C cleanrooms. Facility suits, covering the full length of the arms and the legs, and socks covering the feet, should be worn before entry to change rooms for Grades B and C. Facility suits and socks should not present a risk of contamination to the gowning area or processes.

7.16 Every operator entering Grade B or A areas should gown into clean, sterilized protective garments (including eye coverings and masks) of an appropriate size at each entry. The maximum duration of each garment use should be defined as part of the garment qualification.

7.17 Garments and gloves should be changed immediately if they become damaged and present any risk of product contamination. Gloves should be regularly disinfected during operations.

7.18 Clean area clothing should be cleaned in a dedicated laundry facility using a qualified process ensuring that the clothing is not damaged and/or contaminated by fibres and particles during the laundry process. Inappropriate handling and use of clothing will damage fibres and may increase the risk of shedding of particles. After washing and before packing, garments should be visually inspected for damage. The garment management processes should be evaluated and determined as part of the garment qualification program.

7.19 Activities in clean areas that are not critical to the production processes should be kept to a minimum, especially when aseptic operations are in progress. Movement of personnel should be slow, controlled and methodical to avoid excessive shedding of particulates and organisms due to over-vigorous activity. Operators performing aseptic operations should adhere to aseptic technique at all times to prevent changes in air currents that introduce air of lower quality into the critical zone. Movement adjacent to the critical zone should be restricted and the obstruction of the path of the unidirectional (first air) airflow should be avoided. Airflow visualisation studies should be considered as part of the operator's training programme.

8 Production and Specific Technologies

Terminally sterilized products

8.1 Preparation of components and materials should be performed in at least a Grade D cleanroom in order to limit the risk of microbial, pyrogen and particulate contamination, so that the product is suitable for sterilization. Where the product is at a high or unusual risk of microbial contamination (e.g. the product actively supports microbial growth, the product must be held for long periods before filling or the product is not processed mostly in closed vessels), then preparation should be carried out in a Grade C environment. Preparation of ointments, creams, suspensions and emulsions should be carried out in a Grade C environment before terminal sterilization.

8.2 Primary packaging containers and components should be cleaned using validated processes to ensure that particulate, pyrogen and bioburden contamination is appropriately controlled.

8.3 Filling of products for terminal sterilization should be carried out in at least a Grade C environment.

8.4 Where the product is at an unusual risk of contamination from the environment because, for example, the filling operation is slow, the containers are wide necked or are necessarily exposed for more than a few seconds before closing, then the product should be filled in a Grade A zone with at least a Grade C background.

8.5 Processing of the bulk solution should include a filtration step with a microorganism retaining filter, where possible, to reduce bioburden levels and particulates prior to filling into the final product containers and there should be a maximum permissible time between preparation and filling.

8.6 Examples of operations to be carried out in the various grades are given in Table 4.

Table 4: **Examples of operations and grades for terminally sterilized preparation and processing operations**

A	Filling of products, when unusually at risk.
C	Preparation of solutions, when unusually at risk. Filling of products.
D	Preparation of solutions and components for subsequent filling.

Aseptic preparation and processing

8.7 Aseptic preparation and processing is the handling of sterile product, containers and/or devices in a controlled environment in which the air supply, materials and personnel are regulated to prevent microbial, pyrogenic and particulate contamination.

8.8 The aseptic process should be clearly defined. The risks associated with the aseptic process, and any associated requirements, should be identified, assessed and appropriately controlled. The site's CCS should clearly define the acceptance criteria for these controls, requirements for monitoring and the review of their effectiveness. Methods and procedures to control these risks should be described and implemented. Accepted residual risks should be formally documented.

8.9 Precautions to minimize microbial, pyrogenic and particulate contamination should be taken, as per the site's CCS, during the preparation of the aseptic environment, during all processing stages (including the stages before and after bulk product sterilization), and until the product is sealed in its final container. The presence of materials liable to generate particulates and fibres should be minimized in cleanrooms.

8.10 Where possible, the use of equipment such as RABS, isolators or other systems, should be considered in order to reduce the need for critical interventions into the Grade A zone and to minimize the risk of contamination. Robotics and automation of processes can also be considered to eliminate direct human critical interventions (e.g. dry heat tunnel, automated lyophilizer loading, sterilization in place).

8.11 Examples of operations to be carried out in the various environmental grades are given in the Table 5.

Table 5: **Examples of operations and grades for aseptic preparation and processing operations**

Grade A	Critical zone for - Aseptic assembly of filling equipment. - Connections made under aseptic conditions (where sterilized product contact surfaces are exposed) that are post the final sterilizing filter. These connections should be sterilized by steam-in-place whenever feasible. - Aseptic compounding and mixing. - Replenishment of sterile bulk product, containers and closures. - Removal and cooling of unprotected (e.g. with no packaging) items from sterilizers. - Staging and conveying of sterile primary packaging components. - Aseptic filling, sealing of containers such as ampoules, vial closure, transfer of open or partially stoppered vials. - Loading of a lyophilizer.
Grade B	Background support for the Grade A zone (when not in an isolator). - Transport, while protected from the surrounding environment, of equipment, components and ancillary items for introduction into the Grade A zone.
Grade C	- Preparation of solutions to be filtered including weighing.
Grade D	- Cleaning of equipment. - Handling of components, equipment and accessories after washing. - Assembly of cleaned components, equipment and accessories prior to sterilization. - Assembly of closed and sterilized SUS using intrinsic aseptic connectors.

8.12 For sterile products that cannot be filtered, the following should be considered:

i. All product and component contact equipment should be sterilized prior to use.

ii. All raw materials should be sterilized and aseptically added or subsequently sterilized by filtration.

iii. Bulk solutions should be sterilized by a validated process, e.g. by heat, chemical sterilization or via sterile filtration.

iv. All materials added to the sterile bulk product should be sterilized prior to addition.

8.13 The unwrapping, assembly and preparation of sterilized equipment, components and ancillary items and the preparation and filling of the sterile product should be treated as an aseptic process and performed in a Grade A zone with a Grade B background. Where an isolator or RABS is used, the background should be in accordance with paragraphs 4.21 & 4.22.

8.14 Preparation and filling of sterile products such as ointments, creams, suspensions and emulsions should be performed in a Grade A zone with a Grade B background when the product and components are exposed to the environment and the product is not subsequently filtered (via a sterilizing filter) or terminally sterilized. Where an isolator or RABS is used, the background should be in accordance with paragraphs 4.21 & 4.22.

8.15 Aseptic connections should be performed in a Grade A zone with a Grade B background unless subsequently sterilized in place or conducted with validated intrinsic sterile connection devices that minimize any potential contamination from the immediate environment. Where an isolator or RABS is used, the background should be in accordance with paragraphs 4.21 & 4.22. Aseptic connections should be appropriately assessed and their effectiveness verified. For requirements regarding intrinsic sterile connection devices refer to paragraph 8.120.

8.16 Aseptic manipulations (including non-intrinsic aseptic connections) should be minimized through the use of engineering design solutions such as preassembled and sterilized equipment. Whenever feasible, product contact piping and equipment should be pre-assembled, and sterilized in place.

8.17 There should be an authorized list of allowed interventions, both inherent and corrective, that may occur during production. The procedures listing the types of inherent and corrective interventions, and how to perform them, should be updated, as necessary to ensure consistency with the actual manufacturing activities. In the event that an unauthorized intervention is required, details of the intervention conducted should be recorded and fully assessed under the manufacturer's PQS.

8.18 The duration of each aspect of aseptic preparation and processing should be limited to a defined and validated maximum time, including:

i. The holding time between equipment, component, and container cleaning, drying and sterilization.

ii. The holding time for sterilized equipment, components, and containers before use and during filling/assembly.

iii. The holding time for a decontaminated environment, such as the RABS and isolator before and during filling /assembly.

iv. The time between the start of the preparation of a product and its sterilization or filtration through a microorganism-retaining filter (if applicable), through to the end of the aseptic filling process. There should be a maximum permissible time for each product that takes into account its composition and the prescribed method of storage.

v. The holding time for sterilized product prior to filling.

vi. The aseptic processing time.

vii. The filling time.

viii. The maximum exposure time of sterilized containers and closures in the critical processing zone (including filling) prior to closure.

8.19 Aseptic operations (including APS) should be observed at a regular basis by personnel with specific expertise in aseptic processing to verify the correct performance of operations and address inappropriate practices if detected.

Finishing of sterile products

8.20 Open primary packaging containers (including partially stoppered vials or prefilled syringes) should be maintained under Grade A conditions with Grade B background (e.g. Barrier Technology), or under Grade A conditions with physical segregation from operators (e.g. UDAF carts) until the stopper is fully inserted.

8.21 Containers should be closed by appropriately validated methods. Containers closed by fusion, e.g. Blow-fill-seal (BFS), Form-Fill-Seal (FFS), Small and Large Volume Parenteral (SVP & LVP) bags, glass or plastic ampoules, should be subject to 100% integrity testing. Samples of containers closed by other methods should be taken and checked for integrity using validated methods. The frequency of testing should be based on the knowledge and experience of the container and closure systems being used. A scientifically valid sampling plan should be utilized. The sample size should be based on information such as supplier approval, packaging component specifications and process knowledge. It should be noted that visual inspection alone is not considered as an acceptable integrity test method.

8.22 Containers sealed under vacuum (where the vacuum is necessary for the product stability) should be tested for maintenance of vacuum after an appropriate pre-determined period and during shelf life.

8.23 The container closure integrity validation should take into consideration any transportation or shipping requirements that may negatively impact the integrity of the container (e.g. by decompression or temperature extremes).

8.24 Where the equipment used to crimp vial caps can generate large quantities of non-viable particulates, measures to prevent particulate contamination such as locating the equipment at a physically separate station equipped with adequate air extraction should be taken.

8.25 Vial capping can be undertaken as an aseptic process using sterilized caps or as a clean process outside the aseptic core. Where the latter approach is adopted, vials should be protected by Grade A conditions up to the point of leaving the aseptic processing area, and thereafter stoppered vials should be protected with a Grade A air supply until the cap has been crimped. Where capping is a manual process it should be performed under Grade A conditions either in an appropriately designed isolator or into Grade A zone with a Grade B background.

8.26 Where capping of aseptically filled sterile product is conducted as a clean process with Grade A air supply protection, vials with missing or displaced stoppers should be rejected prior to capping. Appropriately qualified, automated methods for stopper height detection should be in place.

8.27 Where human intervention is required at the capping station, appropriate technological and organizational measures should be used to prevent direct contact with the vials and to minimize microbial contamination.

8.28 RABS and isolators may be beneficial in assuring the required conditions and minimizing the microbial contamination associated with direct human interventions into the capping operation.

8.29 All filled containers of parenteral products should be inspected individually for extraneous contamination or other defects. Defect classification and criticality should be determined during qualification and based on risk and historical knowledge. Factors to consider include, but are not limited to, the potential impact of the defect to the patient and the route of administration. Different defect types should be categorized and batch performance analysed. Batches with unusual levels of defects, when compared with routine defect numbers for the process (based on historical and trend data), should lead to an investigation. A defect library should be generated and maintained which captures all known classes of defects. The defect library should be used for the training of production and quality assurance personnel. Critical defects should not be identified during any subsequent sampling and inspection of acceptable containers. Any critical defect identified should trigger an investigation as it indicates a possible failure of the original inspection process.

8.30 When inspection is done manually, it should be performed under suitable and controlled conditions of illumination and background. Inspection rates should be appropriately controlled and qualified. Operators performing the inspection should undergo visual inspection qualification (whilst wearing corrective lenses, if these are normally worn) at least annually. The qualification should be undertaken using appropriate samples from the manufacturer's defect library sets and taking into consideration worst case scenarios (e.g. inspection time, line speed where the product is transferred to the operator by a conveyor system, container size or fatigue at the end of shift) and should include consideration of eyesight checks. Operator distractions should be minimized and frequent breaks, of an appropriate duration, from inspection should be taken.

8.31 Where automated methods of inspection are used, the process should be validated to detect known defects (which may impact the product quality, safety or efficacy) and be equal to, or better than, manual inspection methods. The performance of the equipment should be challenged using representative defects prior to start up and at regular intervals.

8.32 Results of the inspection should be recorded and defect types and numbers trended. Reject levels for the various defect types should also be trended based on statistical principles. Impact to product on the market should be assessed as part of the investigation when adverse trends are observed.

Sterilization

8.33 Where possible, finished product should be terminally sterilized, using a validated and controlled sterilization process, as this provides a greater assurance of sterility than a validated and controlled sterile filtration process and/or aseptic processing. Where it is not possible for a product to undergo terminal sterilization, consideration should be given to using terminal bioburden reduction steps, such as heat treatments (e.g. pasteurization), combined with aseptic process to give improved sterility assurance.

8.34 The selection, design and location of the equipment and cycle/programme used for sterilization should be based on scientific principles and data which demonstrate repeatability and reliability of the sterilization process. Critical parameters should be defined, controlled, monitored and recorded.

8.35 All sterilization processes should be validated. Validation studies should take into account the product composition, storage conditions and maximum time between the start of the preparation of a product or material to be sterilized and its sterilization. Before any sterilization process is adopted, its suitability for the product and equipment, and its efficacy in consistently achieving the desired sterilizing conditions in all parts of each type of load to be processed should be validated notably by physical measurements and where appropriate by biological indicators (BI). For effective sterilization, the whole of the product, and surfaces of equipment and components should be subject to the required treatment and the process should be designed to ensure that this is achieved.

8.36 Particular attention should be given when the adopted sterilization method is not described in the current edition of the Pharmacopoeia, or when it is used for a product which is not a simple aqueous solution. Where possible, heat sterilization is the method of choice.

8.37 Validated loading patterns should be established for all sterilization processes and should be subject to periodic revalidation. Maximum and minimum loads should also be considered as part of the overall load validation strategy.

8.38 The validity of the sterilizing process should be reviewed and verified at scheduled intervals based on risk. Heat sterilization cycles should be revalidated with a minimum frequency of at least annually.

8.39 Routine operating parameters should be established and adhered to for all sterilization processes, e.g. physical parameters and loading patterns.

8.40 There should be mechanisms in place to detect a sterilization cycle that does not conform to the validated parameters. Any failed sterilization or sterilization that deviated from the validated process (e.g. have longer or shorter phases such as heating cycles) should be investigated.

8.41 Suitable BIs placed at appropriate locations may be considered as an additional method to support the validation of the sterilization process. BIs should be stored and used according to the manufacturer's instructions. Where BIs are used to support validation and/or to monitor a sterilization process (e.g. for ethylene oxide), positive controls should be tested for each sterilization cycle. If BIs are used, strict precautions should be taken to avoid transferring microbial contamination to the manufacturing or other testing processes. BI results in isolation do not give assurance of sterilization and should not be used to override other critical parameters and process design elements.

8.42 The reliability of BIs is important. Suppliers should be qualified and transportation and storage conditions should be controlled in order that BI quality is not compromised. Prior to use of a new batch/lot of BIs, the population and identity of the indicator organism of the batch/lot should be verified. For other critical parameters, e.g. D-value, Z- value, the batch certificate provided by the qualified supplier can normally be used.

8.43 There should be a clear means of differentiating products, equipment and components, which have not been subjected to the sterilization process from those which have. Containers used to carry products such as baskets or trays, items of equipment and/or components should be clearly labelled (or electronically tracked) with the material name, product batch number and an indication of whether or not it has been sterilized. Indicators such as autoclave tape, or irradiation indicators may be used, where appropriate, to indicate whether or not a batch (or sub-batch) has passed through a sterilization process. However, these indicators show only that the sterilization process has occurred, they do not indicate product sterility or achievement of the required sterility assurance level.

8.44 Sterilization records should be available for each sterilization run. Each cycle should have a unique identifier. They should be reviewed and approved as part of the batch certification procedure.

8.45 Where possible, materials, equipment and components should be sterilized by validated methods appropriate to the specific material. Suitable protection after sterilization should be provided to prevent recontamination. If sterilized items are not used immediately after sterilization, these should be stored using appropriately sealed packaging. A maximum hold time should also be established. Where justified, components that have been packaged with multiple sterile packaging layers need not be stored in a cleanroom if the integrity and configuration of the sterile pack allows the items to be readily disinfected during transfer by operators into the Grade A zone, (e.g. by the use of multiple sterile coverings that can be removed at each transfer from lower to higher grade). Where protection is achieved by containment in sealed packaging, this packaging process should be undertaken prior to sterilization.

8.46 Where materials, equipment, components and ancillary items are sterilized in sealed packaging and then transferred into the Grade A zone, this should be done using appropriate, validated methods (for example, airlocks or pass-through hatches) with accompanying disinfection of the exterior of the sealed packaging. The use of rapid transfer port technology should also be considered. These methods should be demonstrated to effectively control the potential risk of contamination of the Grade A zone and Grade B area and, likewise, the disinfection procedure should be demonstrated to be effective in reducing any contamination on the packaging to acceptable levels for entry of the item into the Grade B and Grade A areas.

8.47 Where materials, equipment, components and ancillary items are sterilized in sealed packaging or containers, the packaging sealing process should be validated. The validation should consider the integrity of the sterile protective barrier system and the maximum hold time before sterilization and maximum shelf life assigned to the sterilized items. The integrity of the sterile protective barrier system for each of the sterilized items should be confirmed prior to use.

8.48 For materials, equipment, components and ancillary items that are necessary for aseptic processing but cannot be sterilized, an effective and validated disinfection and transfer process should be in place. These items, once disinfected, should be protected to prevent recontamination. These items, and others representing potential routes of contamination, should be included in the environmental monitoring program.

Sterilization by heat

8.49 Each heat sterilization cycle should be recorded either electronically or by hardcopy, on equipment with suitable accuracy and precision. Monitoring and recording systems should be independent of the controlling system (e.g. by the use of duplex/double probes).

8.50 The position of the temperature probes used for controlling and/or recording should be determined during the validation which should include heat distribution and penetration studies and, where applicable, also checked against a second independent temperature probe located at the same position.

8.51 Sufficient time should be allowed for the whole of the load to reach the required temperature before measurement of the sterilizing time-period starts. For sterilization cycles controlled by using a reference probe within the load, specific consideration should be given to ensuring the load probe temperature is controlled within defined temperature range prior to cycle commencement.

8.52 After completion of the high temperature phase of a heat sterilization cycle, precautions should be taken against contamination of a sterilized load during cooling. Any cooling liquid or gas that comes in contact with the product or sterilized material should be sterilized.

8.53 In those cases where parametric release has been authorized, a robust system should be applied to the product lifecycle validation and the routine monitoring of the manufacturing process. This system should be periodically reviewed. Further guidance regarding parametric release is provided in Annex 17.

Moist heat sterilization

8.54 Moist heat sterilization utilises steam or superheated water, typically at lower temperatures and shorter duration than dry heat processes, in order to sterilize a product or article. Moist heat sterilization of hard goods or porous loads is primarily effected by latent heat of condensation of clean steam and the quality of steam is therefore important to provide consistent results. For aqueous liquid-filled containers, energy from moist heat is transferred through conduction and/or convection to the content of the container without direct contact with the autoclave steam. In these cases, time and temperature are the key parameters and steam quality does not have the same impact to the process. Moist heat sterilization processes may be utilized to sterilize or control bioburden (for non-sterile applications) of thermally stable materials, articles or products and is the preferred method of sterilization, where possible. Moist heat sterilization can be achieved using steam, (direct or indirect contact), but also includes other systems such as superheated water systems. Superheated systems are typically used for the terminal sterilization of product in flexible containers where the pressure differentials associated with the steam would cause damage to the primary container.

8.55 For porous cycles (hard goods) time, temperature and pressure should be used to monitor the process. Each item sterilized should be inspected for damage, packaging material integrity and moisture on removal from the autoclave. Any item found not to be fit for purpose should be removed from the manufacturing area and an investigation performed.

8.56 For autoclaves fitted with a drain at the bottom of the chamber, the temperature should be recorded at this position throughout the sterilization period. For steam in place systems, the temperature should be recorded at condensate drain locations throughout the sterilization period.

8.57 Validation of porous cycles should include a calculation of equilibration time, exposure time, correlation of pressure and temperature and maximum temperature range during exposure. Validation of fluid cycles should include temperature, time and/or F_o. These critical processing parameters should be subject to defined limits (including appropriate tolerances) and be confirmed as part of the sterilization validation and routine cycle acceptance criteria.

8.58 Leak tests on the sterilizing system should be carried out periodically (normally weekly) when a vacuum phase is part of the cycle or the system is returned, post-sterilization, to a pressure lower than the environment surrounding the sterilized system.

8.59 There should be adequate assurance of air removal prior to and during sterilization when the sterilization process includes air purging (e.g. porous autoclave loads, lyophilizer chambers). For autoclaves, this should include an air removal test cycle (normally performed on a daily basis) or an air detector system. Loads to be sterilized should be designed to support effective air removal and be free draining to prevent the build-up of condensate.

8.60 The items to be sterilized, other than products in sealed containers, should be dry, wrapped in a material which allows removal of air and penetration of steam and prevents recontamination after sterilization. All loaded items should be dry upon removal from the sterilizer. Load dryness should be confirmed by visual inspection as a part of the sterilization process acceptance.

8.61 If it is necessary to wet equipment using WFI (e.g. ultrafiltration membrane) prior to the sterilization process, then a risk-based assessment should be carried out to demonstrate the acceptable dryness level that will not impact the sterility of the equipment sterilized and the product sterility assurance level. The hold time between the wetting phase and sterilization should be justified and validated.

8.62 Distortion and damage of non-rigid containers that are terminally sterilized, such as containers produced by Blow-Fill-Seal or Form-Fill-Seal technologies, should be prevented by appropriate cycle design and control (for instance setting correct pressure, heating and cooling rates and loading patterns).

8.63 Where steam in place systems are used (e.g. for fixed pipework, vessels and lyophilizer chambers), the system should be appropriately designed and validated to assure all parts of the system are subjected to the required treatment. The system should be monitored for temperature, pressure and time at appropriate locations during routine use to ensure all areas are effectively and reproducibly sterilized. These locations should be demonstrated as being representative of, and correlated with, the slowest to heat locations during initial and routine validation. Once a system has been sterilized by steam in place it should remain integral and held under positive pressure prior to use.

8.64 For systems using superheated water rather than steam, as the sterilizing agent, the heated water should consistently reach all of the required contact points. Initial qualification studies should include temperature mapping of the entire load. There should be routine checks on the equipment to ensure that nozzles (where the water is introduced) are not blocked and drains remain free from debris.

8.65 For the qualification of superheated systems it should be demonstrated that all parts of the load meet the minimum required temperature and that routine monitoring probes are located in the worst case positions identified during the qualification process.

Dry heat sterilization

8.66 Dry heat sterilization is of particular use in the removal of thermally robust contaminants such as pyrogens and is often used in the preparation of components for aseptic filling. The combination of time and temperature to which product, components and equipment are exposed should produce an adequate and reproducible level of lethality and/or pyrogen (endotoxin) inactivation/removal when operated routinely within the established limits.

8.67 Dry heat sterilization/depyrogenation tunnels should be configured to ensure that airflow protects the integrity and performance of the Grade A sterilizing zone by maintaining pressure differentials and airflow through the tunnel from the higher grade area to the lower grade area. Airflow patterns should be visualised and correlated with temperature studies. The impact of any airflow change should be assessed to ensure the heating profile is maintained. All air supplied to the tunnel should pass through at least a HEPA filter and periodic tests should be performed to demonstrate air filter integrity (at least biannually). Any tunnel parts that come into contact with sterilized components should be appropriately sterilized or disinfected. Critical process parameters that should be considered during validation and/or routine processing should include, but may not be limited to:

i. Belt speed or dwell time within the sterilizing zone.

ii. Temperature – minimum and maximum temperatures.

iii. Heat penetration of the material/article.

iv. Heat distribution/uniformity.

v. Airflows – correlated with the heat distribution and penetration studies.

8.68 When a thermal depyrogenation process is used for any component or product contact equipment, validation studies should be performed to demonstrate that the process provides a suitable F_h value and results in a minimum 3 log reduction in endotoxins concentration.

8.69 Containers inoculated with endotoxin should be used during validation and should be carefully managed with a full reconciliation performed. Containers should be representative of the materials normally processed. Endotoxin quantification and recovery efficiency should also be demonstrated through biological measurement.

8.70 Dry heat ovens are typically employed to sterilize or depyrogenate primary packaging components, finished materials or active substances but may be used for other processes. They should be maintained at a positive pressure relative to lower grade areas throughout the sterilization and post sterilization hold process. All air entering the oven should pass through a sterilizing filter. Critical process parameters that should be considered in qualification and/or routine processing should include, but may not be limited to:

i. Temperature.

ii. Exposure period/time.

iii. Chamber pressure (for maintenance of over pressure).

iv. Air speed.

v. Air quality within the oven.

vi. Heat penetration of material/article (slow to heat spots).

vii. Heat distribution/uniformity.

8.71 For dry heat sterilization of starting materials and intermediates, the same principles should be applied. Consideration should also be given to factors affecting heat penetration such as the container type, size and packing matrix.

Sterilization by radiation

8.72 Guidance regarding ionising radiation sterilization can be found within Annex 12.

8.73 Sterilization by radiation is used mainly for the sterilization of heat sensitive materials and products. Ultraviolet irradiation is not an acceptable method of sterilization.

8.74 Validation procedures should ensure that the effects of variations in density of the product and packages are considered.

Sterilization with ethylene oxide

8.75 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 result in the reduction of any residual ethylene oxide (EO) gas and reaction products to defined acceptable limits for the given product or material.

8.76 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, porosity and quantity of packaging materials can significantly affect the process.

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

8.78 Each sterilization cycle should be monitored with suitable BIs, using the appropriate number of test units distributed throughout the load at defined locations that have been shown to be worst case during validation.

8.79 Critical process variables that could be considered as part of the sterilization process validation and routine monitoring include, but are not limited to:

i. EO gas concentration.

ii. EO gas pressure.

iii. Amount of EO gas used.

iv. Relative humidity.

v. Temperature.

vi. Exposure time.

8.80 After sterilization, the load should be aerated to allow EO gas and/or its reaction products to desorb from the packaged product to predetermined levels. Aeration can occur within a sterilizer chamber and/or in a separate aeration chamber or aeration room. The aeration phase should be validated as part of the overall EO sterilization process validation.

Filter sterilization of products which cannot be sterilized in their final container

8.81 If the product cannot be sterilized in the final container, solutions or liquids should be sterilized by filtration through a sterile sterilizing grade filter (with a nominal pore size of 0.22 µm (or less) that has been appropriately validated to obtain a sterile filtrate) and subsequently aseptically filled into a previously sterilized container. The selection of the filter used should ensure that it is compatible with the product and as described in the marketing authorization (refer to paragraph 8.125).

8.82 Suitable bioburden reduction prefilters and/or sterilizing grade filters may be used at multiple points during the manufacturing process to ensure a low and controlled bioburden of the liquid prior to the primary sterilizing grade filter. Due to the potential additional risks of a sterile filtration process, as compared with other sterilization processes, a second filtration through a sterile sterilizing grade filter, immediately prior to filling, should be considered as part of an overall CCS.

8.83 The selection of components for the filtration system and their interconnection and arrangement within the filtration system, including pre-filters, should be based on the critical quality attributes of the product, justified and documented. The filtration system should minimize the generation of fibres and particulates, not cause or contribute to unacceptable levels of impurities, or possess characteristics that otherwise alter the quality and efficacy of the product. Similarly, the filter characteristics should be compatible with the fluid and not be adversely affected by the product to be filtered. Adsorption of product components and extraction/leaching of filter components should be evaluated (refer to paragraph 8.125).

8.84 The filtration system should be designed to:

i. Allow operation within validated process parameters.

ii. Maintain the sterility of the filtrate.

iii. Minimize the number of aseptic connections required between the sterilizing filter and the final filling of the product.

iv. Allow cleaning procedures to be conducted as necessary.

v. Allow sterilization procedures, including sterilization in place, to be conducted as necessary.

vi. Permit in-place integrity testing, of the 0.22 µm sterilizing filter, preferably as a closed system, prior to filtration as necessary. In-place integrity testing methods should be selected to avoid any adverse impact on the quality of the product.

8.85 Sterile filtration of liquids should be validated in accordance with European (or other relevant) Pharmacopeia requirements. Validation can be grouped by different strengths or variations of a product but should be done under worst case conditions. The rationale for grouping should be justified and documented.

8.86 During filter validation, wherever possible, the product to be filtered should be used for bacterial retention testing of the sterilizing filter. Where the product to be filtered is not suitable for use in bacterial retention testing, a suitable surrogate product should be justified for use in the test. The challenge organism used in the bacterial retention test should be justified.

8.87 Filtration parameters that should be considered and established in validation and monitored in routine processing should include, but are not limited to:

i. The wetting fluid used for filter integrity testing should be based on the filter manufacturer's recommendation or the fluid to be filtered. The appropriate integrity test value specification should be established.

ii. If the system is flushed or integrity tested in-situ with a fluid other than the product, appropriate actions are taken to avoid any deleterious effect on product quality.

iii. Filtration process conditions including:

- Fluid pre-filtration holding time and effect on bioburden.
- Filter conditioning, with fluid if necessary.
- Maximum filtration time/total time filter is in contact with fluid.
- Maximum operating pressure.
- Flow rate.
- Maximum filtration volume.
- Temperature.
- The time taken to filter a known volume of bulk solution and the pressure difference to be used across the filter.

Note: Results of these checks should be included in the batch record. Any significant difference in parameters from those validated to those observed during routine manufacturing should be noted and investigated.

8.88 The integrity of the sterilized filter assembly should be verified by integrity testing before use, to check for damage and loss of integrity caused by the filter preparation prior to use. A sterilizing grade filter that is used to sterilize a fluid should be subject to a non-destructive integrity test post-use prior to removal of the filter from its housing. Test results should correlate to the microbial retention capability of the filter established during validation. Examples of tests that are used include bubble point, diffusive flow, water intrusion or pressure hold test. It is recognized that pre-use post sterilization integrity testing (PUPSIT) may not always be possible after sterilization due to process constraints (e.g. the filtration of very small volumes of solution). In these cases, an alternative approach may be taken providing that a thorough risk assessment has been performed and compliance is achieved by the implementation of appropriate controls to mitigate any risk of non-sterility. Points to consider in such a risk assessment should include but are not be limited to:

i. In depth knowledge and control of the sterilization process to ensure that the potential for damage to the filter is minimized.

ii. In depth knowledge and control of the supply chain to include:
   - Contract sterilization facilities.
   - Defined transport mechanisms.
   - Packaging of the sterilized filter, to prevent damage to the filter during transportation and storage.

iii. In depth process knowledge such as:
   - The specific product type, including particulate burden and whether there exists any risk of impact on filter integrity values, such as the potential to alter integrity testing values and therefore prevent the detection of a non-integral filter during a post-use filter integrity test.
   - Pre-filtration and processing steps, prior to the sterilizing filter, which would remove particulate burden and clarify the product prior to the sterile filtration.

8.89 The integrity of critical sterile gas and air vent filters (that are directly linked to the sterility of the product) should be verified by testing after use, with the filter remaining in the filter assembly.

8.90 The integrity of non-critical air or gas vent filters should be confirmed and recorded at appropriate intervals. Where gas filters are in place for extended periods such as vent filters, integrity testing should be carried out pre and post-use. The maximum duration of use should be specified and monitored based on risk (e.g. considering the maximum number of uses and sterilization cycles permitted).

8.91 For gas filtration, attention should be paid to avoiding unintended moistening or wetting of the filter or filter equipment. This can be achieved by the use of hydrophobic filters.

8.92 If the sterilizing filtration process has been validated as a system consisting of multiple filters to achieve the sterility for a given fluid, the filtration system is considered to be a single sterilizing unit and all filters within the system should satisfactorily pass integrity testing after use.

8.93 In a redundant filtration system (where a second filter is present as a backup but the sterilizing process is validated as only requiring one filter), post-use integrity test of the primary sterilizing filter should be performed and if demonstrated to be integral, then a post-use integrity test of the secondary filter is not necessary. However, in the event of a failure of the post-use integrity test on the primary filter, a risk assessment should be carried out to determine the acceptability of performing a post-use integrity test on the secondary (redundant) filter.

8.94 Bioburden samples should be taken from the bulk product and immediately prior to the final sterile filtration. Systems for taking samples should be designed so as not to introduce contamination.

8.95 Liquid sterilizing filters should be discarded after the processing of a single lot and the same filter should not be used for more than one working day unless such use has been validated.

8.96 Where campaign manufacture of a product has been appropriately justified in the CCS and validated, the filter user should:

i. Assess and document the risks associated with the duration of filter use for the sterile filtration process for a given fluid.

ii. Conduct and document effective validation and qualification studies to demonstrate that the duration of filter use for a given sterile filtration process and for a given fluid does not compromise performance of the sterilizing filter or filtrate quality.

iii. Document the maximum validated duration of use for the filter and implement controls to ensure that filters are not used beyond the validated maximum duration. Records of these controls should be maintained.

iv. Implement controls to ensure that filters contaminated with fluid or cleaning agent residues, or considered defective in any other way, are removed from use.

Form-Fill-Seal

8.97 Form-Fill-Seal (FFS) units include blow moulding from thermoplastic granulate and thermoforming from thermoplastic film, typically known as Blow-Fill-Seal (BFS) and Vertical-Form-Fill-Seal (VFFS), respectively. VFFS process is an automated filling process, typically for terminally sterilized products, that may utilize a single or dual web system which constructs the primary container out of a flat roll of thermoplastic film while simultaneously filling the formed bags with product and sealing the filled bags in a continuous process. All such containers are considered to be closed through sealing by fusion and, as such, fall under the requirement to perform 100% integrity testing (refer to paragraph 8.21).

8.98 Process parameters relating to seal integrity should be qualified and appropriately controlled.

8.99 Critical parameters include, but are not limited to:

i. Seal strength.

ii. Seal uniformity.

iii. Sealing temperatures.

iv. Sealing pressures.

v. Sealing times.

vi. Dwell time for filling.

8.100 Seal strength and uniformity should be monitored routinely.

8.101 The controls identified during qualification should be in alignment with the site's CCS. Aspects to be considered include but are not limited to:

i. Determination of the boundaries of the critical zone.

ii. Environmental control and monitoring, both of the machine and the background in which it is placed.

iii. Integrity testing of the product filling lines.

iv. Integrity testing of the cooling system.

v. Duration of the batch or filling campaign.

vi. Control of polymer starting material (including resin pellets).

vii. Cleaning-in-place and sterilization-in-place of equipment in direct contact to the formulation (product filling lines); sterilization-in-place of sterile air pathways.

Blow-Fill-Seal

8.102 Blow-Fill-Seal (BFS) units are purpose built machines in which, in one continuous operation, containers are formed from a thermoplastic granulate, filled and then sealed by one automatic machine. Air that makes contact with critical surfaces of the container during extrusion, formation or sealing of the moulded container should undergo appropriate filtration.

8.103 For shuttle type equipment used for aseptic filling, the area between parison cutting and mould sealing should be covered by a flow of filtered air to provide Grade A conditions at the critical zone. The equipment should be installed in at least a Grade C environment, provided that Grade A/B clothing is used. The filling environment should meet Grade A for viable and non-viable limits at rest and the viable limit only when in operation.

8.104 For rotary-type equipment, used for aseptic filling, the filling environment should be designed to meet Grade A conditions. Other sterility assurance controls such as monitoring of critical parameters and alarms during each batch and parison support filter integrity testing should be considered.

8.105 The environmental control and monitoring program should take into consideration the moving parts and complex airflow paths generated by the BFS process and the effect of the high heat outputs of the process, e.g. by performing smoke studies and/or other equivalent studies. Environmental monitoring should be applied taking into consideration elements such as air-filter configuration, air-filter integrity, cooling systems integrity, equipment design and installation.

8.106 Blow-Fill-Seal equipment used for the manufacture of products which are terminally sterilized should be installed in at least a Grade D environment. The conditions at the point of fill should comply with the environmental requirements of paragraphs 8.3 and 8.4.

8.107 External particulate and microbial contamination of the polymer should be prevented by appropriate design, control, and maintenance of the polymer storage, sampling and distribution systems. The capability of the extrusion system to provide appropriate sterility assurance for the moulded container should be fully understood and validated. The sampling frequency, the bioburden and, where applicable, endotoxins levels of the raw polymer should be defined and controlled within the CCS.

8.108 Interventions requiring cessation of filling and/or extrusion, moulding and sealing and, where required, re-sterilization of the filling machine should be clearly defined and well described in the aseptic filling procedure, and included in the APS (refer to paragraphs 9.36, 9.37 and 9.38).

8.109 The moulds used to form containers are considered critical equipment and any changes or modification to moulds should result in an assessment of finished product container integrity, and should be supported by validation.

Lyophilization

8.110 Lyophilization is a critical process step and all activities that can affect the sterility of the product or material need to be regarded as extensions of the aseptic processing of the sterilized product. The lyophilization equipment and its processes should be designed to ensure that product or material sterility is maintained during lyophilization by preventing microbial and particulate contamination between the filling of products for lyophilization, and completion of lyophilization process. All control measures in place should be determined by the site's CCS.

8.111 The sterilization of lyophilizers and associated equipment, (e.g. trays, vial support rings) should be validated and holding times between sterilization cycles appropriately challenged during aseptic process simulations. The lyophilizer should be sterilized regularly, based on system design. Re-sterilization should be performed following maintenance or cleaning. Sterilized lyophilizers and associated equipment should be protected from contamination after sterilization.

8.112 Lyophilizers that are manually loaded or unloaded should normally be sterilized before each load. For lyophilizers loaded by automated closed systems or located within systems that exclude operator intervention, the frequency of sterilization should be justified and documented as part of the CCS.

8.113 The integrity of the lyophilizer system should be maintained following sterilization and during use. The filter used to maintain lyophilizer integrity should be sterilized before each use of the system and its integrity testing results should be part of the batch certification. The frequency of vacuum/leak integrity testing of the chamber should be documented and the maximum permitted leakage of air into the lyophilizer should be specified and checked at the start of every cycle.

8.114 Lyophilization trays should be checked regularly to ensure that they are not misshapen or damaged.

8.115 Points to consider for the design of loading (and unloading, where the lyophilised material is not in a sealed container (e.g. open tray dried materials), include but are not limited to:

i. The loading pattern within the lyophilizer should be specified and documented.

ii. The transfer of partially closed containers to a lyophilizer should be undertaken under Grade A conditions at all times and handled in a manner designed to minimize direct operator intervention. Technologies such as conveyor systems, portable transfer systems (e.g. clean air transfer carts, portable unidirectional airflow workstations) should be used to ensure that the cleanliness of the system used to transfer the partially closed containers is maintained). Alternatively, where supported by validation, containers closed in the Grade A zone and not reopened whilst in the Grade B may be used to protect partially stoppered vials (e.g. sealed sterilized trays).

iii. Airflow patterns should not be adversely affected by transport devices and venting of the loading zone.

iv. Unsealed containers (such as partially stoppered vials) should be maintained under Grade A conditions and should normally be separated from operators by physical barrier technology or any other appropriate measures.

v. Where seating of the stoppers is not completed prior to opening the lyophilizer chamber, product removed from the lyophilizer should remain under Grade A conditions during subsequent handling.

vi. Utensils used during transfer to and loading and unloading of the lyophilizer (such as trays, bags, placing devices, tweezers, etc.) should be subject to a validated sterilization process.

Closed systems

8.116 Closed systems can be single use systems (i.e. disposable systems) and fixed systems (such as vessels with fixed pipework). Guidance in this section is equally applicable to both systems.

8.117 The use of closed systems can reduce the risk of extraneous contamination such as microbial, particulate and chemical from the adjacent environment. Closed systems should always be designed to reduce the need for, and complexity of manual interventions.

8.118 It is critical to ensure the sterility of all product contact surfaces of closed systems used for aseptic processing. The design and selection of any closed system used for aseptic processing should ensure maintenance of sterility. Connection of sterile equipment (e.g. tubing / pipework) to the sterilized product pathway after the final sterilizing filter should be designed to be connected aseptically (e.g. by intrinsic aseptic connectors or fusion systems).

8.119 Appropriate measures should be in place to ensure the integrity of components used in aseptic connections. The means by which this is achieved should be determined and captured in the CCS. Appropriate system integrity tests should be considered when there is a risk of compromising product sterility. Supplier assessment should include the collation of data in relation to potential failure modes that may lead to a loss of system sterility.

8.120 The background in which closed systems are located should be based on their design and the processes undertaken. For aseptic processing and where there are any risks that system integrity may be compromised, the system should be located in a Grade A zone. If the system can be shown to remain integral at every usage (e.g. via pressure testing and/or monitoring) then a lower classified area may be used. If the closed system is opened (e.g. for maintenance of a bulk manufacturing line) then this should be performed in a classified area appropriate to the materials (e.g. Grade C for terminally sterilization processes, or Grade A for aseptic processing) or be subject to further cleaning and disinfection (and sterilization in case of aseptic processes).

Single use systems (SUS)

8.121 SUS are those technologies used in manufacture of sterile products which are used as an alternative to reusable equipment. SUS can be individual components or made up of multiple components such as bags, filters, tubing, connectors, valves, storage bottles and sensors.

8.122 There are some specific risks associated with SUS which should be assessed as part of the CCS. These risks include but are not limited to:

i. The interaction between the product and product contact surface (such as adsorption, or the formation of leachables and extractables).

ii. The fragile nature of the system compared to fixed reusable systems.

iii. The increase in the number and complexity of manual operations (including inspection and handling of the system) and connections made.

iv. The complexity of the assembly.

v. The performance of the pre-use integrity test for sterilizing grade filters (refer to paragraph 8.88).

vi. The risk of holes and leakage.

vii. The potential for compromising the system at the point of opening the outer packaging.

viii. The risk of particulate contamination.

8.123 Sterilization processes for SUS should be validated and shown to have no adverse impact on system performance.

8.124 Assessment of suppliers of disposable systems including sterilization is critical to the selection and use of these systems. For sterile SUS, verification of sterility should be performed as part of the supplier qualification and on receipt and use of each unit.

8.125 The adsorption and reactivity of the product with product contact surfaces should be evaluated under process conditions.

8.126 The extractable and leachable profile of the SUS and any impact on the quality of the product especially where the system is made from polymer-based materials should be evaluated. An assessment should be carried out for each component to evaluate the applicability of the extractable profile data. For components considered to be at high risk from leachables, including those that may absorb processed materials or those with extended material contact times, an assessment of leachable profile studies, including safety concerns, should be taken into consideration. If applying simulated processing conditions, these should accurately reflect the actual processing conditions and be based on a scientific rationale.

8.127 SUS should be designed to maintain integrity throughout processing under the intended operational conditions. Attention to the structural integrity of the single use components is necessary where these may be exposed to more extreme conditions (e.g. freezing and thawing processes) either during routine processing or transportation. This should include verification that intrinsic aseptic connections (both heat sealed and mechanically sealed) remain integral under these conditions.

8.128 Acceptance criteria should be established and implemented for SUS corresponding to the risks or criticality of the products and its processes. On receipt, each piece of SUS should be checked to ensure that they have been manufactured, supplied and delivered in accordance with the approved specification. A visual inspection of the outer packaging (e.g. appearance of exterior carton, product pouches), label printing, and review of attached documents (e.g. certificate of conformance and proof of sterilization) should be carried out and documented prior to use.

8.129 Critical manual handling operations of SUS such as assembly and connections should be subject to appropriate controls and verified during the APS.

9 Viable and non-viable environmental & process monitoring

General

9.1 The site's environmental and process monitoring program forms part of the overall CCS and is used to monitor the controls designed to minimize the risk of microbial and particulate contamination. It should be noted that the reliability of each of the elements of the monitoring system (viable, non-viable and APS) when taken in isolation is limited and should not be considered individually to be an indicator of asepsis. When considered together, their reliability is dependent on the design, validation and operation of the system that they are monitoring.

9.2 This program is typically comprised of the following elements:

i. Environnemental monitoring – non-viable particles.

ii. Environmental and personnel monitoring – viable particles.

iii. Aseptic process simulation (aseptically manufactured product only).

9.3 The information from these systems should be used for routine batch certification and for periodic assessment during process review or investigation. This applies for both terminal sterilization and aseptic processes, however, the criticality of the impact may differ depending upon the product and process type.

Environmental monitoring

9.4 Risk assessments should be performed in order to establish a comprehensive environmental monitoring program, i.e. sampling locations, frequency of monitoring, monitoring method used and incubation conditions (e.g. time, temperature(s), aerobic and/or anaerobic conditions). These risk assessments should be conducted based on detailed knowledge of; the process inputs and final product, the facility, equipment, specific processes, the operations involved, historical monitoring data, monitoring data obtained during qualification and knowledge of typical microbial flora isolated from the environment. Consideration of other information such as air visualization studies should also be included. These risk assessments should be reviewed regularly in order to confirm the effectiveness of the site's environmental monitoring program. The monitoring program should be considered in the overall context of the trend analysis and the CCS for the site.

9.5 Routine monitoring of cleanrooms, clean air equipment and personnel should be performed in operation throughout all critical stages, including equipment set-up.

9.6 The monitoring of Grade A zones should demonstrate the maintenance of aseptic processing conditions during critical operations. Monitoring should be performed at locations posing the highest risk of contamination to the sterile equipment surfaces, container, closures and product. The selection of monitoring locations and the orientation and positioning of sampling devices should be justified and appropriate to obtain reliable data from the critical zones.

9.7 Sampling methods should not pose a risk of contamination to the manufacturing operations.

9.8 Appropriate alert levels and action limits should be set for the results of viable and non-viable particle monitoring. Alert levels should be established based on results of cleanroom qualification tests or trend data and should be subject to periodic review.

9.9 Alert levels for Grade A (non-viable particles only) Grade B, Grade C and Grade D should be set such that adverse trends (e.g. a numbers of events or individual events that indicate a deterioration of cleanliness) are detected and addressed.

9.10 Monitoring procedures should define the approach to trending. Trends can include, but are not limited to:

i. Increasing numbers of action limit or alert level breaches.

ii. Consecutive breaches of alert levels.

iii. Regular but isolated breaches of action limits that may have a common cause, for example single excursions that always follow planned preventative maintenance.

iv. Changes in microbial flora type and numbers and predominance of specific organisms. Particular attention should be given to objectionable organisms or those that can be difficult to control such as spore-forming microorganisms.

9.11 The monitoring of Grade C and D cleanrooms in operation should be performed based on data collected during qualification and historical data to allow effective trend analysis. The requirements of alert levels and action limits will depend on the nature of the operations carried out. Action limits may be more stringent than those listed in Table 6 and Table 7.

9.12 If action limits are exceeded, operating procedures should prescribe a root cause investigation, an assessment of the potential impact to product and requirements for corrective and preventive actions. If alert levels are exceeded, operating procedures should prescribe assessment and follow-up, which should include consideration of an investigation and/or corrective actions to avoid any further deterioration of the environment.

9.13 Results from environmental monitoring should be considered when reviewing batch documentation for finished product batch certification.

Environmental monitoring- non-viable particles

9.14 Non-viable particulate monitoring systems should be established to obtain data for assessing potential contamination risks and to ensure the maintenance of the environment for sterile operations in a qualified state.

9.15 The limits for environmental monitoring of airborne particulate concentrations for each graded area are given in Table 6.

Table 6: Limits for airborne particulate concentration for the monitoring of non-viable contamination.

Grade	Maximum limits for particulates ≥ 0.5 μm/m³		Maximum limits for particulates ≥ 5 μm/m³	
	at rest	in operation	at rest	in operation
A	3 520	3 520	29	29
B	3 520	352 000	29	2 900
C	352 000	3 520 000	2 900	29 000
D	3 520 000	Not defined[a]	29 000	Not defined[a]

[a] For Grade D, in operation limits are not defined. The company should establish in operation limits based on a risk assessment and on historical data, where applicable.

Note 1: The particulate limits given in the table for the "at rest" state should be achieved after a short "clean up" period (defined during qualification with a guidance value of 15 to 20 minutes) in an unmanned state, after the completion of operations (refer to paragraph 4.30 and 4.31).

Note 2: With regards to the monitoring of airborne particulates ≥5 μm particulate concentration, the limit of 29 (Grade A) is selected due to the limitations of monitoring equipment. Alert levels should be set based on historical data, such that frequent sustained counts below the action limit which may be indicative of system contamination or deterioration should trigger an investigation. For the Grade A zone and Grade B area the importance of monitoring the ≥5 μm particulates is to identify negative trends as defined in the manufacturer's CCS.

9.16 For the Grade A zone, particulate monitoring should be undertaken for the full duration of critical processing, including equipment assembly.

9.17 The Grade A zone should be monitored continuously (for particulates ≥0.5 and ≥5 μm) and with a suitable sample flow rate (at least 28 litres (1ft^3) per minute) so that all interventions, transient events and any system deterioration is captured. The system should frequently correlate each individual sample result with the limits in Table 6 at such a frequency that any potential excursion can be identified and responded to in a timely manner. Alarms should be triggered if alert levels are exceeded. Procedures should define the actions to be taken in response to alarms including the consideration of additional microbial monitoring.

9.18 It is recommended that a similar system be used for Grade B area although the sample frequency may be decreased. The Grade B zone should be monitored at such a frequency and with suitable sample size that the programme captures any increase in levels of contamination and system deterioration. If alert or action levels are exceeded, alarms should be triggered.

9.19 The selection of the monitoring system should take into account any risk presented by the materials used in the manufacturing operation (for example, those involving live organisms, powdery products or radiopharmaceuticals) that may give rise to biological or chemical hazards.

9.20 In the case where contaminants are present due to the processes involved and would potentially damage the particle counter or present a hazard (e.g. live organisms, powdery products and radiation hazards), the frequency and strategy employed should be such as to assure the environmental classification both prior to and post exposure to the risk. An increase in viable particle monitoring should be considered to ensure comprehensive monitoring of the process. Additionally, monitoring should be performed during simulated operations. Such operations should be performed at appropriate intervals. The approach should be defined in the CCS.

9.21 The size of monitoring samples taken using automated systems will usually be a function of the sampling rate of the system used. It is not necessary for the sample volume to be the same as that used for formal classification of cleanrooms and clean air equipment. Monitoring sample volumes should be justified.

9.22 The occasional indication of macro particulate counts, especially ≥ 5 µm, may be considered to be false counts due to electronic noise, stray light, coincidence, etc. However, consecutive or regular counting of low levels may be indicative of a possible contamination event and should be investigated. Such events may indicate early failure of the room air supply filtration system, filling equipment failure, or may also be diagnostic of poor practices during machine set-up and routine operation.

9.23 Monitoring conditions such as frequency, sampling volume or duration, alert levels and action limits and corrective actions (including an investigation) should be established in each manufacturing area based on data generated during the initial qualification process, ongoing routine monitoring and periodic review of data.

Environmental and personnel monitoring-viable particles

9.24 Where aseptic operations are performed, microbial monitoring should be frequent using a combination of methods such as settle plates, volumetric air sampling, glove, gown and surface sampling (e.g. swabs and contact plates). The method of sampling used should be justified within the CCS and should be demonstrated not to have a detrimental impact on Grade A and B airflow patterns.

9.25 Monitoring should include sampling of personnel at periodic intervals during the process. Sampling of personnel should be performed in such a way that it will not compromise the process. Particular consideration should be given to monitoring personnel following involvement in critical interventions and on each exit from the Grade B cleanroom.

9.26 Viable particle monitoring should also be performed within the cleanrooms when normal manufacturing operations are not occurring (e.g. post disinfection, prior to start of manufacturing, on completion of the batch and after a shutdown period), and in associated rooms that have not been used, in order to detect potential incidents of contamination which may affect the controls within the cleanrooms. In case of an incident, additional sample locations may be used as a verification of the effectiveness of a corrective action (i.e. cleaning and disinfection).

9.27 Continuous viable air monitoring in the Grade A zone (e.g. air sampling or settle plates) should be undertaken for the full duration of critical processing, including equipment (aseptic set-up) assembly and filling operations. A similar approach should be considered for Grade B cleanrooms based on the risk of impact on the aseptic processing. The monitoring should be performed in such a way that all interventions, transient events and any system deterioration would be captured and any risk caused by interventions of the monitoring operations is avoided.

9.28 The adoption of suitable rapid or automated monitoring systems should be considered by manufacturers in order to expedite the detection of microbiological contamination issues and to reduce the risk to product. These rapid and automated microbial monitoring methods may be adopted after validation has demonstrated their equivalency or superiority to the established methodology.

9.29 Sampling methods and equipment used should be fully understood and procedures should be in place for the correct operation and interpretation of results obtained. The recovery efficiency of the sampling methods chosen should be qualified.

9.30 Action limits for viable particle contamination are shown in Table 7

Table 7: **Maximum action limits for** viable particle **contamination**

Grade	**Air sample cfu/m^3**	**Settle plates (diam. 90 mm) cfu/4 hours [(a)]**	**Contact plates (diam. 55mm), cfu/ plate [(c)]**	**Glove print, Including 5 fingers on both hands cfu/ glove**
A	No growth[(b)]			
B	10	5	5	5
C	100	50	25	-
D	200	100	50	-

[(a)] Settle plates should be exposed for the duration of operations and changed as required after 4 hours (exposure time should be based on validation including recovery studies and it should not have any negative effect on the suitability of the media used). Individual settle plates may be exposed for less than 4 hours.

[(b)] It should be noted that for Grade A, any growth should result in an investigation.

[(c)] Contact plate limits apply to equipment room and gown surfaces within the Grade A zone and Grade B area. Routine gown monitoring is not normally required for Grade C and D areas, depending on their function.

Note 1: It should be noted that the types of monitoring methods listed in the table above are examples and other methods can be used provided they meet the intent of providing information across the whole of the critical process where product may be contaminated (e.g. aseptic line set-up, filling and lyophilizer loading).

Note 2: Limits are applied using cfu throughout the document. If different or new technologies are used that present results in a manner different from cfu, the manufacturer should scientifically justify the limits applied and where possible correlate them to cfu.

9.31 Microorganisms detected in Grade A zone and Grade B area should be identified to species level and the potential impact of such microorganisms on product quality (for each batch implicated) and overall state of control should be evaluated. Consideration should also be given to the identification of microorganisms detected in Grade C and D areas (for example where action limits or alert levels are exceeded or where atypical or potentially objectionable microorganisms are recovered). The approach to organism identification and investigation should be documented.

9.32 Personnel gloves (and any part of the gown that may potentially have direct impact on the product sterility (e.g. the sleeves if these enter a critical zone) should be monitored for viable contamination after critical operations and on exit from the cleanroom. Other surfaces should be monitored at the end of an operation.

9.33 Microbial monitoring of personnel in the Grade A zone and Grade B area should be performed to assess their aseptic behaviour. Where filling operations are manual in nature e.g. hand filling, the process in its entirety may be considered as one critical intervention. In these cases, the frequency of microbial monitoring of gowning should be based on scientific principles and justified as part of the CCS. Where monitoring is routinely performed by manufacturing personnel, consideration should be given to periodic monitoring under the supervision of the quality unit.

Aseptic process simulation (APS) (also known as media fill)

9.34 Periodic verification of the effectiveness of the controls in place for aseptic processing should include a process simulation test using a sterile nutrient media and/or surrogate in place of the product. Selection of an appropriate nutrient media should be made based on the ability of the media and/or surrogate to imitate product characteristics at all processing stages. Where processing stages may indirectly impact the viability of any introduced microbial contamination, (e.g. sterile aseptically produced semi-solids, powders, solid materials, microspheres, liposomes and other formulations where product is cooled or heated or lyophilized), alternative procedures that represent the operations as closely as possible can be developed and justified. Where surrogate materials, such as buffers, are used in parts of the process simulation, the surrogate material should not inhibit the growth of any potential contamination.

9.35 The process simulation test should imitate as closely as possible the routine aseptic manufacturing process and include all the critical manufacturing steps, specifically:

i. Process simulation tests should assess all aseptic operations performed subsequent to the sterilization and decontamination cycles of materials utilised in the process to the point where the container is sealed.

ii. For non-filterable formulations, any additional aseptic steps should be assessed.

iii. Where aseptic manufacturing is performed under an inert atmosphere, the inert gas should be substituted with air in the process simulation unless anaerobic simulation is intended.

iv. Processes requiring the addition of sterile powders should use an acceptable surrogate material in containers identical to those used in the process under evaluation.

v. Separate simulations of individual unit operations (e.g. processes involving drying, blending, milling and subdivision of a sterile powder) should generally be avoided. Any use of individual simulations should be supported by a documented justification and ensure that the sum total of the individual simulations continues to fully cover the whole process.

vi. The process simulation procedure for lyophilized products should represent the entire aseptic processing chain including filling, transport, loading, chamber dwell, unloading and sealing under specified, documented and justified conditions representing worst case operating parameters.

vii. The lyophilization process simulation should duplicate all aspects of the process, except those that may affect the viability or recovery of contaminants. For instance, boiling-over or actual freezing of the solution should be avoided. Factors to consider in determining APS design include, where applicable:

- The use of air to break vacuum instead of nitrogen.

- Replicating the maximum interval between sterilization of the lyophilizer and its use.

- Replicating the maximum period of time between sterilization and lyophilization.

- Quantitative aspects of worst case situations, e.g. loading the largest number of trays, replicating the longest duration of loading where the chamber is open to the environment.

9.36 The process simulation testing should take into account various aseptic manipulations and interventions known to occur during normal production as well as worst case situations, including:

i. Inherent interventions representative of the routine process at the maximum accepted frequency per number of filled units (e.g. loading of vials into a lyophilizer).

ii. Corrective interventions, that occur frequently during routine production, in a representative number and with the highest degree of acceptable intrusion (e.g. correcting jammed stoppers).

9.37 Interventions should not be designed or selected to justify poor process or facility design or to assess unacceptable interventions that rarely occur and which should lead to a thorough investigation and product assessment when they do occur.

9.38 In developing the process simulation test plan, consideration should be given to the following:

i. Identification of worst case conditions covering the relevant variables, such as container size and line speed, and their impact on the process. The outcome of the assessment should justify the variables selected.

ii. Determining the representative sizes of container/closure combinations to be used for validation. Bracketing or matrix approach may be considered for validation of the same container/closure configuration for different products where process equivalence is scientifically justified.

iii. The volume filled per container, which should be sufficient to ensure that the media contacts all equipment and component surfaces that may directly contaminate the sterile product. The volume used should provide sufficient headspace to support potential microbial growth and ensure that turbidity can be detected during inspection.

iv. Maximum permitted holding times for sterile product and associated sterile components and equipment exposed during the aseptic process.

v. The method of detection of microbial contamination should be scientifically justified to ensure that any contamination is detectable.

vi. The selected nutrient media should be capable of growing a designated group of reference microorganisms as described by the relevant pharmacopeia and suitably representative local isolates and supporting recovery of low numbers of these microorganisms.

vii. The requirement for substitution of any inert gas used in the routine aseptic manufacturing process by air unless anaerobic simulation is intended. In these situations, inclusion of occasional anaerobic simulations as part of the overall validation strategy should be considered (refer to paragraph 9.35 point iii).

viii. The process simulation should be of sufficient duration to challenge the process, the operators that perform interventions, shift changes and the capability of the processing environment to provide appropriate conditions for the manufacture of a sterile product.

ix. Where the manufacturer operates different shifts then the APS should be designed to capture specific factors (e.g. for those manufacturing during a night or extended shift, fatigue should be considered).

x. Simulating normal aseptic manufacturing interruptions where the process is idle (e.g. shift changeovers, recharging dispensing vessels, introduction of additional equipment, etc.).

xi. Ensuring that environmental monitoring is conducted as required for routine production, and throughout the entire duration of the process simulation.

xii. Where campaign manufacturing occurs, such as in the use of Barrier Technologies or manufacture of sterile active substances, consideration should be given to designing and performing the process simulation so that it simulates the risks associated with both the beginning and the end of the campaign and demonstrating that the campaign duration does not pose any risk. The performance of "end of production or campaign APS" may be used as additional assurance or investigative purposes; however, their use should be justified in the CCS and should not replace routine APS. If used, it should be demonstrated that any residual product does not negatively impact the recovery of any potential microbial contamination.

9.39 For sterile active substances, batch size should be large enough to represent routine operation, simulate intervention operation at the worst case, and cover potential contact surfaces. In addition, all the simulated materials (surrogates or growth medium) should be subjected to microbial evaluation. The simulation materials should be sufficient to satisfy the evaluation of the process being simulated and should not compromise the recovery of micro-organisms.

9.40 Process simulation tests should be performed as part of the initial validation, with at least three consecutive satisfactory simulation tests that cover all working shifts that the aseptic process may occur in, and after any significant modification to operational practices, facilities, services or equipment (e.g. modification to the HVAC system, equipment, major facility shut down, changes to process, number of shifts and numbers of personnel etc.). Normally, process simulation tests (periodic revalidation) should be repeated twice a year (approximately every six months) for each aseptic process, each filling line and each shift. Each operator should participate in at least one successful APS annually. Consideration should be given to performing an APS after the last batch prior to shut down, before long periods of inactivity or before decommissioning or relocation of a line.

9.41 Where manual operation (e.g. aseptic compounding or filling) occurs, each type of container, container closure and equipment train should be initially validated with each operator participating in at least 3 consecutive successful APS and revalidated with one APS approximately every 6 months for each shift. The APS batch size should mimic that used in the routine aseptic manufacturing process.

9.42 The number of units processed (filled) for APS tests should be sufficient to effectively simulate all activities that are representative of the aseptic manufacturing process. Justification for the number of units to be filled should be clearly captured in the PQS. Typically, a minimum of 5000 to 10000 units are filled. For small batches (e.g. those under 5000 units), the number of containers for media fill should at least equal the size of the production batch.

9.43 Filled APS units should be agitated, swirled or inverted before incubation to ensure contact of the media with all interior surfaces in the container. Units with cosmetic defects or those who have gone through non-destructive in process control checks should be identified and incubated. Units discarded during the process simulation and not incubated should be comparable with units discarded during a routine fill. Examples may include those normally discarded after the set-up process or due to an intervention or where the integrity of the unit is compromised as would be identified by the routine inspection process for the product.

9.44 Where processes have materials that contact the product contact surfaces but are then discarded, the discarded material should be simulated with nutrient media and be incubated as part of the APS, unless it can be clearly demonstrated that this waste process would not impact the sterility of the product.

9.45 Filled APS units should be incubated in a clear container to ensure visual detection of microbial growth. Where the product container is not clear (i.e. amber glass, opaque plastic), clear containers of identical configuration may be substituted to aid in the detection of contamination. When a clear container of identical configuration cannot be substituted, a suitable method for the detection of microbial growth should be developed and validated. Microorganisms isolated from contaminated units should be identified to at least genus, and to the species level when practical, to assist in the determination of the likely source of the contaminant. The selection of the incubation conditions and duration should be scientifically justified and validated to provide an appropriate level of sensitivity of detection of microbial contamination.

9.46 Filled APS units should be incubated without unnecessary delay to achieve the best possible recovery of potential contamination.

9.47 On completion of incubation:

i. Filled APS units should be inspected by staff, who have been trained and qualified in the visual inspection procedures, under conditions similar to those for visual inspection, that facilitate the identification of any microbial contamination.

ii. Samples of these units should undergo positive control by inoculation with a suitable range of reference organisms and local isolates.

9.48 The target should be zero growth. Any contaminated unit should result in a failed process simulation and the following actions should occur:

i. An investigation to determine the most probable root causes.

ii. Determination and implementation of appropriate corrective measures.

iii. A sufficient number of successful, consecutive repeat media fills (normally a minimum of 3) should be conducted in order to demonstrate that the process has been returned to a state of control.

iv. A prompt review of all appropriate records relating to aseptic production since the last successful APS. The outcome of the review should include a risk assessment of potential sterile breaches in batches manufactured since the last successful process simulation. All other batches not released to the market should be included in the scope of the investigation. Any decision regarding their release status should consider the investigation outcome.

v. All products that have been manufactured on a line subsequent to a process simulation failure should be quarantined until a successful resolution of the process simulation failure has occurred.

vi. Production should resume only after completion of successful revalidation.

9.49 APS should be carefully observed by personnel with specific expertise in aseptic processing to assess the correct performance of operations and address inappropriate practices if detected.

9.50 Where results indicate that an operator may have failed qualification, actions to limit the operator's activities, until retrained and requalified, should be taken.

9.51 An aseptic process or filling should be subject to a repeat of the initial validation when:

i. The specific aseptic process has not been in operation for an extended period of time.

ii. There is a change to the process, equipment, procedures or environment that has the potential to affect the aseptic process or an addition of new product containers or container-closure combinations.

9.52 All process simulation runs should be fully documented and include a reconciliation of units processed (e.g. units filled, incubated, not incubated, and rejected). All interventions performed during the process simulations should be recorded, including the start and end of each intervention. All microbial monitoring data as well as other testing data should be recorded in the APS batch record.

10 Quality Control (QC)

10.1 It is important that there are personnel with appropriate training and experience in microbiology and knowledge of the process to support the design of the manufacturing process, environmental monitoring regime and any investigation assessing the impact of microbiologically linked events to the safety of the sterile product.

10.2 Specifications for raw materials, components and products should include requirements for microbial quality when the need for this has been indicated by monitoring and/or by the CCS.

10.3 The bioburden assay should be performed on each batch for both aseptically filled product and terminally sterilized products and the results considered as part of the final batch review. There should be defined limits for bioburden immediately before the sterilizing filter or the terminal sterilization process, which are related to the efficiency of the method to be used. Samples should be taken to be representative of the worst case scenario (e.g. at the end of hold time). Where overkill sterilization parameters are set for terminally sterilized products, bioburden should be monitored at suitable scheduled intervals.

10.4 A pre-sterilization bioburden monitoring program for the product and components should be developed to support parametric release. The bioburden should be performed for each batch. The sampling locations of filled units before sterilization should be based on a worst case scenario and be representative of the batch. Any organisms found during bioburden testing should be identified and their impact on the effectiveness of the sterilizing process determined. Where appropriate, the level of pyrogen (endotoxins) should be monitored.

10.5 The sterility test applied to the finished product should only be regarded as the last in a series of control measures by which sterility is assured. It cannot be used to assure sterility of a product that does not meet its design, procedural or qualification parameters. The test should be validated for the product concerned.

10.6 The sterility test should be performed under aseptic conditions. Samples taken for sterility testing should be representative of the whole of the batch but should in particular include samples taken from parts of the batch considered to be most at risk of contamination, for example:

i. For products which have been filled aseptically, samples should include containers filled at the beginning, middle and end of the batch and after any significant intervention (e.g. interventions where the integrity of a barrier is breached (open door)) or an operator intervention into critical zones.

ii. For products which have been heat sterilized in their final containers, samples taken should be representative of the worst case locations (e.g. the potentially coolest or slowest to heat part of each load).

iii. For products that are lyophilized, samples taken from different lyophilization loads.

Note: Where the manufacturing process results in sub-batches (e.g. for terminally sterilized products) then sterility samples from each sub-batch should be taken and a sterility test for each sub-batch performed. Consideration should also be given to performing separate testing for other finished product tests.

10.7 For some products it may not be possible to perform a sterility test prior to release because the shelf life of the product is too short to allow completion of a sterility test. In these cases, the CCS should clearly capture the identified risks, the additional considerations of design of the process and additional monitoring required to mitigate the identified risks.

10.8 Any process (e.g. Vaporized Hydrogen Peroxide or VH202, Ultra Violet) used to decontaminate the external surfaces of sterility samples prior to testing should not negatively impact the sensitivity of the test method.

10.9 Media used for environmental monitoring and APS should be tested for its growth promotion capability, in accordance with a formal written program.

10.10 Environmental monitoring data and trend data generated for classified areas should be reviewed as part of product batch certification. A written plan should be available that describes the actions to be taken when data from environmental monitoring are found out of trend or exceeding the established limits. For products with short shelf life, the environmental data for the time of manufacture may not be available; in these cases, the certification should include a review of the most recent available data. Manufacturers of these products should consider the use of rapid monitoring systems.

10.11 Where rapid and automated microbial methods are used for general manufacturing purposes, these methods should be validated for the product(s) or processes concerned.

Glossary

Airlock – An enclosed space with interlocked doors, constructed to maintain air pressure control between adjoining rooms (generally with different air cleanliness standards). The intent of an airlock is to preclude ingress of particulate matter and microorganism contamination from a lesser controlled area.

Action limit – An established relevant measure (e.g. microbial, or airborne particulate limits) that, when exceeded, should trigger appropriate investigation and corrective action based on the investigation.

Alert level – An established relevant measure (e.g. microbial, or airborne particulate levels) giving early warning of potential drift from normal operating conditions and validated state, which does not necessarily give grounds for corrective action but triggers appropriate scrutiny and follow-up to address the potential problem. Alert levels are established based on historical and qualification trend data and periodically reviewed. The alert level can be based on a number of parameters including adverse trends, individual excursions above a set limit and repeat events.

Aseptic processing room – A room in which one or more aseptic activities or processes are performed.

Aseptic Process Simulation (APS) –A simulation of the entire aseptic formulation and filling process in order to determine the capability of the process to assure product sterility.

Asepsis – A state of control attained by using an aseptic work area and performing activities in a manner that precludes microbial contamination of the exposed sterile product.

Bacterial retention testing – This test is performed to validate that a filter can remove bacteria from a gas or liquid. The test is usually performed using a standard organism, such as *Brevundimonas diminuta* at a minimum concentration of 10^7 Colony Forming Units/cm^2.

Barrier – A physical partition that affords aseptic processing area (usually Grade A) protection by separating it from the background environment. Such systems frequently use in part or totally the Barrier Technologies known as RABS or isolators.

Bioburden – The total number of microorganisms associated with a specific item such as personnel, manufacturing environments (air and surfaces), equipment, product packaging, raw materials (including water), in-process materials, or finished products.

Biological Indicator (BI) – A population of microorganisms inoculated onto a suitable medium (e.g. solution, container or closure) and placed within a sterilizer or load or room locations to determine the sterilization or disinfection cycle efficacy of a physical or chemical process. The challenge microorganism is selected and validated based upon its resistance to the given process. Incoming lot D value, microbiological count and purity define the quality of the BI.

Blow-Fill-Seal (BFS) – A technology in which containers are formed from a thermoplastic granulate, filled with product, and then sealed in a continuous, integrated, automatic operation. The two most common types of BFS machines are the Shuttle type (with Parison cut) and the Rotary type (Closed Parison) types.

Classified area – An area that contains a number of cleanrooms (see cleanroom definition).

Cleaning – A process for removing contamination e.g. product residues and disinfectant residues.

Clean area – An area with defined particulate and microbiological cleanliness standards usually containing a number of joined cleanrooms.

Cleanroom – A room designed, maintained, and controlled to prevent particulate and microbial contamination of drug products. Such a room is assigned and reproducibly meets an appropriate air cleanliness level. Grade A will be referred to as Grade A zone.

Cleanroom classification – A method of assessing the level of air cleanliness against a specification for a cleanroom or clean air equipment by measuring the non-viable airborne particulate concentration.

Cleanroom qualification – A method of assessing the level of compliance of a classified cleanroom or clean air equipment with its intended use.

Closed system – A system in which the sterile product is not exposed to the surrounding environment. For example, this can be achieved by the use of bulk products holders (such as tanks or bags) that are connected to each other by pipes or tubes as a system, with the system being sterilized after the connections are made. Examples of these can be (but are not limited to) large scale reusable systems, such as those seen in active substance manufacturing, or disposable bag and manifold systems, such as those seen in the manufacture of biological products. Closed systems, when used in this document, does not refer to systems such as RABS or isolator systems which are referred to as Barrier Technologies.

Colony Forming Unit (CFU) – A microbiological term that describes a single detectable colony that originates from one or more microorganisms. Colony forming units are typically expressed as cfu per ml for liquid samples, and cfu per cm^2 for samples captured on solid medium such as settle or contact plates.

Contamination – The undesired introduction of impurities of a microbiological nature (quantity and type of microorganisms, pyrogens), or of foreign particulate matter, into or onto a raw material, intermediate, active substance or drug product during production, sampling, packaging or repackaging, storage or transport with the potential to adversely impact product quality.

Contamination Control Strategy (CCS) – A planned set of controls for microorganisms, pyrogens and particulates, derived from current product and process understanding that assures process performance and product quality. The controls can include parameters and attributes related to active substance, excipient and drug product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control.

Corrective intervention – An intervention that is performed to correct or adjust an aseptic process during its execution. These may not occur with the same frequency in the routine aseptic process. Examples include such as clearing component jams, stopping leaks, adjusting sensors, and replacing equipment components. Corrective measures should be taken to reduce their extent and frequency.

Critical surfaces – Surfaces that may come directly into contact with, or directly affect, a sterile product or its containers or closures. Critical surfaces are rendered sterile prior to the start of the manufacturing operation, and sterility is maintained throughout processing.

Critical zone – A location within the aseptic processing area in which product and critical surfaces are exposed to the environment.

Critical intervention – An intervention (corrective or inherent) into the critical zone.

D value – The value of a parameter of sterilization (duration or absorbed dose) required to reduce the number of viable organisms to 10 per cent of the original number.

Dead leg – Length of non-circulating pipe (where fluid may remain static) that is greater than 3 internal pipe diameters.

Decommission – When a process, equipment or cleanroom are closed where they will not be used again.

Decontamination – The overall process of removal or reduction of any contaminants (chemical, waste, residue or microorganisms) from an area, object, or person. The method of decontamination used (e.g. cleaning, disinfection, sterilization) should be chosen and validated to achieve a level of cleanliness appropriate to the intended use of the item decontaminated.

Depyrogenation – A process designed to remove or inactivate pyrogenic material (e.g. endotoxins) to a specified minimum quantity.

Disinfection – The process by which the reduction of the number of microorganisms is achieved by the irreversible action of a product on their structure or metabolism, to a level judged to be appropriate for a defined purpose.

Endotoxin – A pyrogenic product (e.g. lipopolysaccharide) present in the bacterial cell wall. Endotoxin can lead to reactions in patients receiving injections ranging from fever to death.

Extractables - Chemical entities that migrate from the surface of the process equipment, exposed to an appropriate solvent at extreme conditions, into the product or material being processed.

First Air – Refers to filtered air that has not been interrupted by items (such as operators) with the potential to add contamination to the air prior to reaching the critical zone.

Form-Fill-Seal (FFS) – Similar to Blow fill Seal, this involves the formation of a large tube formed from a flexible packaging material, in the filling machine, and generally the tube is filled to form the bags.

Gowning qualification – A program that establishes, both initially and on a periodic basis, the capability of an individual to don the complete sterile gown in an aseptic manner.

Grade A air supply – Air which is passed through a filter qualified as capable of producing Grade A non-viable quality air, but where there is no requirement to perform continuous non-viable monitoring or meet Grade A viable monitoring limits and the area itself is not classified. Specifically used for the protection of fully stoppered vials where the cap has not been crimped and the equipment and engineering systems that have a direct impact on product quality.

HEPA filter - High efficiency particulate air filter with 0.3 µm particulate retaining efficiency of no less than 99.95 percent according to the relevant norms (e.g. EN 1822)..

Inherent interventions – An intervention that is an integral part of the aseptic process and is required for either set-up, routine operation and/or monitoring (e.g. aseptic assembly, container replenishment, environmental sampling, etc.). Inherent interventions are required by procedure or work instruction for the execution of the aseptic process.

Integrity test - A test to confirm that a filter (product, gas or HVAC filter) retain their retentive properties and have not been damaged during handling, installation or processing.

Intrinsic Sterile Connection device – A device that reduces the risk of contamination during the connection process; these can be mechanical or fusion sealing.

Isokinetic sampling head – A sampling head designed to disturb the air as little as possible so that the same particulates go into the nozzle as would have passed the area if the nozzle had it not been there i.e. the sampling condition in which the mean velocity of the air entering the sample probe inlet is nearly the same (± 20 percent) as the mean velocity of the airflow at that location.

Isolator – A decontaminated unit, with an internal work zone meeting Grade A conditions that provides uncompromised, continuous isolation of its interior from the external environment (e.g. surrounding cleanroom air and personnel). There are two major types of isolators

i. Closed isolator systems exclude external contamination of the isolator's interior by accomplishing material transfer via aseptic connection to auxiliary equipment, rather than use of openings to the surrounding environment. Closed systems remain sealed throughout operations.
ii. Open isolator systems are designed to allow for the continuous or semi-continuous ingress and/or egress of materials during operations through one or more openings. Openings are engineered (e.g. using continuous overpressure) to exclude the entry of external contaminant into the isolator.

Leachables – Chemical entities that migrate into products from the product contact surface of the process equipment or containers under normal condition of use and/or storage.

Local Isolates – Suitably representative microorganisms of the site that are frequently recovered through environmental monitoring within the classified zone/areas especially Grade A zone and Grade B area, personnel monitoring or positive sterility test results.

Lyophilization – A physical-chemical drying process designed to remove solvents, by way of sublimation, from both aqueous and non-aqueous systems, primarily to achieve product or material stability. Lyophilization is synonymous to the term freeze-drying.

Manual Filling – A filling process where operator intervention is required to complete the filling of each container (e.g. as occurs during aseptic compounding operations).

Operator - Any individual participating in the processing operation, including line set-up, filler, maintenance, or other personnel associated with manufacturing activities.

Overkill sterilization – A process that is sufficient to provide at least a 12 log reduction of microorganisms having a minimum D value of 1 minute.

Pass-through hatch – Synonymous with airlock (refer to airlock definition) but typically smaller in size.

Pyrogen – A substance that induces a febrile reaction in a patient.

Rapid transfer system (RTP) – A System used for the transfer of items into RABS and isolators that minimize the risk to the critical zone. An example would be a rapid transfer container with an alpha/beta port.

Raw material – Any ingredient intended for use in the manufacture of a sterile product, including those that may not appear in the final drug product.

Restricted Access Barrier System (RABS) – System that provides an enclosed, but not sealed, environment meeting defined cleanroom conditions (for aseptic processing Grade A, (but where used for non-sterile applications can be lesser grade) and using a rigid-wall enclosure and air overspill to separate its interior from the surrounding environment. The inner surfaces of the RABS are disinfected and decontaminated with a sporicidal agent. Operators use gloves, half suits, rapid transfer systems (RTPs) and other integrated transfer ports to perform manipulations or convey materials to the interior of the RABS. Depending on the design, doors are rarely or never opened:

i. Active RABS: integral HEPA-filtered air supply.

ii. Passive RABS: air supply by ceiling mounted HEPA-filters.

iii. Closed RABS: where the air is vented in return ducts within the cabinet.

iv. Open RABS: Where there are vents in the barrier that allow air to move from the Grade A zone to the Grade B area.

Single Use Systems (SUS) – Systems in which product contact components are used only once (i.e. single use components) to replace reusable equipment such as stainless steel transfer lines or bulk containers. SUS covered in this document are those that are used in manufacturing processes of sterile products (e.g. sterile active substance, sterile bio bulk, sterile finished dosage), and are typically made up of disposable components such as bags, filters, tubing, connectors, storage bottles and sensors.

Sporicidal agent – An agent that destroys bacterial and fungal spores when used in sufficient concentration for specified contact time. It is expected to kill all vegetative microorganisms.

Sterile Product – For purpose of this guidance, sterile product refers to one or more of the sterilized elements exposed to aseptic conditions and ultimately making up the sterile active substance or finished sterile product. These elements include the containers, closures, and components of the finished drug product. Or, a product that is rendered sterile by a terminal sterilization process.

Sterilizing grade filter – A filter that, when appropriately validated, will remove a defined microbial challenge from a fluid or gas producing a sterile effluent. Usually such filters have a pore size equal or less than 0.22 µm (for the purposes of this document 0.2 µm and 0.22 µm are used interchangeably and deemed equivalent).

Terminal Sterilization – The application of a lethal sterilizing agent or conditions to a product within a sealed container to achieve a predetermined sterility assurance level (SAL) of 10^{-6} or better (i.e. the theoretical probability of there being a single viable microorganism present on or in a sterilized unit is equal to or less than 1×10^{-6} (one in a million)).

Turbulent airflow – Air that is not unidirectional. Turbulent air in cleanrooms should flush the cleanroom via mixed flow dilution and ensure maintenance of acceptable air quality.

Unidirectional airflow – An airflow moving in a single direction, in a robust and uniform manner, and at sufficient speed, to reproducibly sweep particulates away from the critical processing or testing area.

Unidirectional Airflow Unit (UDAF) – A cabinet supplied with filtered unidirectional airflow (previously referred to as a Laminar Airflow Unit or LAF).

Vertical-Form-Fill-Seal (VFFS) – An automated filling process, typically for terminally sterilized products, that may utilize a single or dual web system which constructs the primary container out of a flat roll of thermoplastic film while simultaneously filling the formed bags with product and sealing the filled bags in a continuous process.

Worst case – A set of conditions encompassing processing limits and circumstances, including those within standard operating procedures, that pose the greatest chance of process or product failure (when compared with ideal conditions). Such conditions have the highest potential to, but do not necessarily always induce, product or process failure.

Water system – A system for producing, storing and distributing water, usually compliant to a specific pharmacopeia grade e.g. purified and water for injection (WFI).