1. Introduction

The objectives of this guidance document are to provide the basic concepts for the assurance of sterility and related manufacturing controls to manufacturers of sterile drug products and to the regulatory personnel responsible for pharmaceutical inspections. The quality of the sterile drug products themselves is to be ensured as well.

This document was designed as a guidance for the aseptic processing of parenteral drugs; however, its basic concepts may also be useful for the manufacture of ophthalmic solutions and other sterile drug products. The concepts and descriptions contained in this guidance may be superseded by other processes or procedures of manufacture that are justifiably comparable or more stringent [except for the MHLW ordinance, "Regulations for Manufacturing Control and Quality Control of Medicinal Products and Quasi-Medicinal Products" (No. 179, 2004; "GMP regulation"), and other regulatory requirements, notifications, and issues], so long as the quality of the drug product is ensured.

2. Glossary

2.1 Acceptance criteria

Established minimum and maximum criteria for acceptance of results of test defined in qualification protocol.

2.2 Action level

Established criteria of microbial or airborne particle level that, when exceeded, should trigger appropriate investigation and corrective action based on the investigation.

2.3 Air cleanliness level

A quality which indicates the condition of cleanliness of a monitored item, expressed as number of particles larger than 0.5 μm permitted per m^3. It is classified in grades A, B, C, and D according to the required particulate number in the air.

2.4 Air lock

A small room with interlocked doors, constructed to maintain air pressure control between adjoining rooms (generally with different air cleanliness standards). The intent of an aseptic processing airlock is to preclude ingress of particulate matter and microorganism contamination from a lesser controlled area. The air balance for the bio-safety facility should be established and maintained to ensure that airflow is from areas of least- to greater contamination.

2.5 Alert level

Established criteria of microbial or airborne particle level (and microbial species if necessary) giving early warning of potential drift from normal conditions. Such conditions are not necessarily grounds for definitive corrective action but which require follow-up investigation.

2.6 Aseptic filling

A Part of aseptic processing where sterilized products are filled and/or packaged into sterile containers and closed under Grade A area.

2.7 Aseptic processing

A method of producing sterile products in which sterile bulk drug or sterile raw materials are compounded and filled into sterile containers in a controlled environment, in which the air supply, materials, equipments and personnel are regulated to control microbial and particulate contamination to acceptable levels under Grade A or B conditions.

2.8 APA: aseptic processing area

Controlled environments, in which the air supply, materials, equipments and personnel are regulated to control microbial and particulate number to acceptable levels. APA is consisted of "critical (processing) area" and "direct support area".

2.9 Barrier

A physical partition to protect direct intervention of operating personnel in a controlled environment.

2.10 Batch/lot

A defined quantity of a product processed in a single process or series of processes within specified limits so that it could be expected to be homogeneous.

2.11 Bioburden

Population of viable microorganisms (bacteria and fungi) which may be present in non-sterile drugs or materials including intermediate products and raw materials.

2.12 BI: biological indicator

Microbiological test system providing defined resistance to a specified sterilization process under defined conditions to be used as an indicator for the sterilization cycle efficacy.

2.13 Calibration

Set of operations which establish under specified conditions the relationship between values indicated by a measuring system, or values represented by a recorder or a controller, and the corresponding values of that quantity obtained from an official reference standard. Limits for acceptance of the results of measuring should be established.

2.14 Change control

Formal assessment and determination of the appropriateness of a proposed alteration to product, process, or procedure.

2.15 Change control system

A formal system planned and designed to assess all changes that might affect the quality of pharmaceutical product to be intended to ensure the maintenance of process control.

2.16 CI: chemical indicator

Test system that reveals change in one or more process variables based on a chemical or physical change resulting from exposure to a sterilization process.

2.17 Cleaning

Removal of contamination from an item to the extent necessary for further processing or for intended use.

2.18 Clean area

An area maintained and controlled to prevent contamination with foreign matter and microbe of drug products, with defined particle and microbiological cleanliness standards. For the purposes of this document, this term is synonymous with manufacturing area for aseptic products.

2.19 CFU: colony forming unit

Visible growth of microorganisms arising from a single cell or multiple cells.

2.20 Critical area

A limited processing area where sterilized containers, raw materials, intermediate products or the surface of equipments which come into contact with sterilized product may be exposed to environment. This area is also called as "critical processing area." The level of the environmental cleanliness of this area is commonly referred to as Grade A.

2.21 Critical processing

A process that may cause variation in the quality of the pharmaceutical product.

2.22 Culture condition

Stated combination of conditions, including the type of medium and the period and temperature of incubation, used to promote microbiological growth.

2.23 Decontamination

A process that reduces or removes contaminating substances to a defined acceptance level by reproducible method.

2.24 DQ: design qualification

Documented verification that the requirements for new facilities, systems, or equipment as developed from research and technological knowledge of the industrial-scale manufacture of a product is scientifically and adequately covered by the basic design of the equipment to be used for actual manufacture. This qualification is routinely performed by comparing design specifications and design drawings.

2.25 Direct support area

A background area directly supporting the critical area. Sterilized products are not directly exposed to the environment in this area. This quality of the environment is commonly referred to as Grade B.

2.26 Disinfection

A process by which surface bioburden is reduced to a safe level or eliminated.

2.27 D value

A value indicating the extinct rate of microorganism. The time or dosage required to achieve inactivation of 90% of a population (one tenth of the survival rate) of the test microorganism under stated exposure conditions.

2.28 Endotoxin

Lipopolysaccharide constituting of outer membrane of Gram negative bacteria and may have pyrogenic reactions and other biological activities to humans.

2.29 Environmental monitoring program

A system to plan, organize and implement all the activities to achieve and maintain the required levels of air and surface cleanliness in the manufacturing areas. The intent is to manufacture aseptic drug products in high quality level, by foreseeing deterioration of environments in manufacturing areas, preventing bad influence to the quality of products, and performing appropriate cleanliness control through a proper monitoring of the manufacturing environment.

2.30 Filter

Porous material through which a liquid or a gas is passed to remove viable and non-viable particles.

2.31 Finished product

A product that has undergone all stages of production, including packaging in its final container and labeling.

2.32 Gas filter

Hydrophobic filters intended to remove microorganisms and particulates from gases (including compressed air).

2.33 HEPA filter: high efficiency particulate air filter

Filters with a minimum efficiency of 99.97% for ≥0.3μm particle size as determined by test.

2.34 HVAC system: heating ventilation and air condition system

An air handling system including heating, ventilation, and air conditioning.

2.35 Indirect supporting area

An area where containers, raw materials, and unsterilized intermediate products are exposed to the environment and where materials and equipment used for aseptic processing are cleaned.

2.36 IQ; installation qualification

Documented verification that the new installation of equipment or changes to existing equipment comply with design specifications and meet those required by the manufacturer.

2.37 Integrity test for containers

Test for confirming container's closure integrity as a part of stability testing for sterile products until the use.

2.38 Integrity test for filter

A non-destructive test which is used to predict the functional performance of a filter.

2.39 Isolator

A sealed and sterilized enclosure capable of preventing ingress of contaminants by means of total physical interior/exterior separation, which takes place through HEPA or ULPA filters.

2.40 Leak test

A pressure hold test should be performed to verify that leak of air into a freeze-dryer under reduced pressure remains within the specified limits. Usually, the interior pressure of the freeze-dryer is reduced to a predetermined vacuum level and then pressure changes are tracked over time to obtain the magnitude of leakage per unit of time. Leaks from other equipment and devices are also checked by measuring pressure drop under increased pressure over a specified period of time or by other appropriate methods.

2.41 Maintenance

Combination of all technical and associated administrative actions intended to retain an item at/or restore it to a state in which it can perform it's required function.

2.42 Manufacturer

A company that carries out at least one step of manufacture.

2.43 MSDS: material safety data sheet

A specific document that shows important physical and chemical characteristics of a chemical or product to alert a user, transporter or other interested party to potential safety hazards that may be associated with the material. An MSDS is a legal requirement in Japan for all aspects of commerce involving chemicals.

2.44 Media fills

One of the processing validations employed to evaluate the propriety of the aseptic processing of pharmaceutical products using sterile media instead of actual product.

2.45 Microorganism

General term for bacteria, fungi, protozoa and virus. Microorganism indicates only bacteria and fungi in this text

2.46 OQ: operational qualification

Documented verification that the equipment to be used for actual manufacture, which is properly installed or changed following installation qualification and necessary calibration, is assured to function in accordance with intended design specifications under anticipated operational conditions.

2.47 Overkill sterilization

A process which is sufficient to provide at least a 12 log reduction of microorganisms having a minimum D value of 1.0 minute, regardless of bioburden count in the product being sterilized or the resistance of the objective microorganisms to the sterilization.

2.48 PQ: performance qualification

Documented verification that the equipment, manufacturing procedures, supporting utilities, etc. are adequate to effectively and consistently produce a product based on its approved specifications and manufacturing methods—by functioning as required by its specifications, the equipment used in the manufacture is capable of exhibiting its capacity as designed and intended when operated according to the manufacturing procedures established through appropriate performance tests; and hence that the product can be manufactured in intended quality.

2.49 Process parameter

Specified value for a process variable.

2.50 Processing area

An area in which actions such as cultivation, extraction/ purification, weighing of raw materials, washing and drying of containers and stoppers, preparation of solutions, filling, sealing and packaging are performed, including the gowning area.

2.51 Product

General term used to describe raw materials, intermediate products and finished products.

2.52 Production

All operations involved in the preparation of a pharmaceutical product, from receipt of materials, through processing and packaging, to completion of the finished product.

2.53 Pure steam

Saturated steam that is generally produced by a pure steam generator and will then be condensed into such high grades of water as purified water or water for injection based upon Pharmacopoeia.

2.54 Sterilizing filter

Either hydrophilic or hydrophobic filter to perform as required should be demonstrated through bacterial challenge testing. The filters should retain specified numbers of indicator bacteria and provide a sterile effluent or gas in a specified pharmaceutical liquid under specified conditions. The nominal pore size of the filters ranges from 0.20 to 0.22 μm.

2.55 Quality system

Organizational structure, procedures, processes and resources needed to implement quality management.

2.56 SOP: standard operating procedure

An authorized written procedure giving instructions for performing operations not necessarily specific to a given product or material but of a more general nature (e.g., equipment operation, maintenance and cleaning; validation; cleaning of premises and environmental control; sampling and inspection). Certain SOPs may be used to supplement product-specific master and batch production documentation.

2.57 Sterile

Free from viable microorganisms.

2.58 SAL: sterility assurance level

Probability of a single viable microorganism being present in a product unit after exposure to the proper sterilization process, expressed as 10^{-n}.

2.59 Sterilization

A process that destroys or eliminates all viable microbes used to render a product free from viable microorganisms.

2.60 System

A regulated pattern of interacting activities and techniques that are united to form an organized whole.

2.61 Terminal sterilization

A process whereby a product is sterilized in its final container or packaging, and which permit the measurement and evaluation of quantifiable microbial lethality. In general, a sterility assurance level should be less than 10^{-6}.

2.62 Unidirectional airflow

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

2.63 Validation

A documented act of proving that facilities and equipment, procedure, process or methods for manufacturing raw materials, operations, systems and quality control consistently leads to the predetermined results.

2.64 Working shift

Scheduled period of work or production, usually less than 12 hours in length, during which operations are conducted by a single defined group of workers.

2.65 Worst case conditions

A set of conditions encompassing upper and lower processing limits and circumstances, including those within standard operating procedures, that pose the greatest chance of process or product failure when compared to ideal conditions.

3. Quality System

The quality system for the aseptic manufacturing of sterile drug products should allow for the establishment, implementation, and maintenance of an efficient and adequate quality control system. It will also allow for adequate maintenance of all necessary records.

3.1 General Requirements

1) General

The quality system should comprise an organizational structure, written procedures and manufacturing processes, and the resources and activities necessary to assure compliance with the requirements for aseptically manufactured sterile drug products as stated in this guideline.

All activities related to quality, including those for sterility assurance, should be clearly identified and documented. Manufacturers who aseptically manufacture sterile drug products should establish a quality system to develop and properly implement procedures for the prevention of microbial contamination during processing. The quality system should include investigation procedures that identify deficiencies in aseptic processing methods and evaluate other abnormalities or deviations from the established control parameters and standards. The verification system to ensure the adequacy of corrective and preventative actions to be taken, should such deviations occur, and follow-up activities after implementation of such actions should be also included in the system.

2) Scope

This guideline is applicable to facilities where aseptically processed drug products are manufactured and to quality control systems related to all aspects of the manufacture of sterile drug products. Factors addressed by this document include environmental control, laboratory control related to sterile drug products, quality control of aseptic processing, validation, and control systems of manufacturing processes, and quality systems such as proper documentation of records and change control procedures.

3) Document control

Operating procedures, instructions/records, deviation controls, change controls, and an investigation system for out-of-specification (OOS) test results should be prepared and maintained to fulfill the requirements for drug product sterility assurance.

4) Risk management

Quality risk management systems for the prevention of contamination with microorganisms, endotoxins, and foreign matter should be employed and implemented. Quality risk management systems should include procedures for risk assessment based on the analysis and evaluation of factors affecting sterility, and endotoxin and foreign matter contamination. Verification of risk control procedures for demonstrating the reliability of risk reduction should also be included.

5) Qualification of aseptic processing environment

Environmental parameters of the processing area should be established and qualified. Based on the qualification results, the manufacturer should also establish a program for the monitoring of environmental conditions as well as for the maintenance of the air handling system.

6) Qualification of aseptic processing equipment

The qualification of the aseptic processing facility and equipment used for the manufacture of sterile drug products in the processing area as well as other equipment that may affect aseptic processing should be established and implemented. Based on the results of the qualification, a program for the maintenance and monitoring of the facility and equipment should also be established.

7) Prospective validation and periodic review of process control

Process validation that simulates all processes and activities related to the sterility of drug products should be conducted. Such processes and activities are actions to achieve sterility of drug products based on designs and operations supported by scientific evidence. A set of process control programs should be established based on the validation.

8) Periodic revalidation

A process simulation program should be included in the periodic revalidation.

9) Time limitation for aseptic manufacturing operations

The manufacturing from initial preparation of a drug solution to filtration and sterilization should be conducted as quickly as possible. An acceptable time frame up to the completion of the filling and sealing processes should be established, taking into account the composition of each drug product, the manufacturing processes, and the storage conditions.

10) Cleaning and disinfection of the facility and equipment

A program for the cleaning and disinfection of the facility and equipment should be established taking the potential development of drug-resistant microorganisms into account. Cleaning and disinfection must be recorded and retained. A program for cleaning and disinfection should be established depending on the cleanliness requirements of each production area. It is recommended that the program be developed with due review of the bacterial isolates identified in each manufacturing environment.

11) Material flow

Appropriate procedures for avoiding microbial contamination of processing areas or rooms used for the manufacture of sterile drug products from sources such as raw materials, other components for production, or containers/closures should be established by identifying material flow and, as appropriate, by establishing disinfection and sterilization procedures.

12) Gowning and personnel entry/exit procedures

Reliable measures should be developed to control the potential for microbial contamination of the processing area or rooms for the manufacture of sterile drug products that could be caused by personnel. Gowning procedures and the direction or method of entry/exit from the manufacturing areas should be standardized.

13) Change control

The assurance of sterility should include scientific evidence that a change in standard procedures would not have any negative impact on the sterility of drug products. Any change should be evaluated through qualification and validation procedures, and, wherever possible, control parameters should be identified and established based on the results of risk assessment to control risks inherent to such a change.

14) Calibration

A calibration program should be established and implemented that defines the calibration frequency and accuracy requirements of the instruments and devices used for measurement, inspection, and control of the manufacturing process and analytical equipment used for quality testing.

3.2. Routine Monitoring and Control

1) An environmental monitoring program should be established and implemented based on the results of environmental qualification testing done on the sterile drug product processing area.
2) Cleaning and disinfection of the sterile drug product processing area should be conducted periodically or on an as-needed basis. It should be verified that the processing area meets predefined environmental control specifications.
3) A maintenance program should be established and implemented based on qualification testing and validation results.
4) A validated process control program should be implemented.
5) Periodic revalidation should be carried out according to the predetermined interval.

3.3. Validation

The manufacture of sterile drug products via aseptic processing can be achieved through the well-harmonized application of hardware, such as well-designed facilities and equipment, and software, such as operating procedures and control systems and programs. The qualification of the aseptic processing environment, the qualification of equipment to be used, and process validation should provide assurance that the integrity of the drug products (safety, efficacy, and uniformity of quality) throughout the manufacturing process, as well as their sterility, will be ensured based on scientific rationale and methodology. The aseptic processing of sterile drug products carries various contamination risk factors that cannot be completely identified and removed during the process development, equipment or operating procedure design stages. Eventually, the qualification and validation procedures will need to be designed, programmed, and implemented for the commercial manufacturing process system as a whole. The production of aseptically processed sterile drug products requires the science-based assessment and eventual elimination of contamination risks in aseptic processes such as filling and sterilization, maintenance of the cleanliness of the processing environment, entire manufacturing processes, and the layout and structures of facilities and equipment at the actual production site.

The fundamental requirement is to control the manufacturing process through validated operating procedures and process parameters. When attempts are made to streamline operating procedures, the proposed alterations, which may include such changes as the omission of one or more process parameters or the shortening of process duration, should be assessed for possible risks, and the proposed changes should be justified by scientific rationale and revalidated as appropriate. If control parameters are to be deleted, revalidation of the proposed changes is not required if the analysis of actual production records supports the deletion, if other existing control parameters compensate for the deleted ones, or if the validity of the remaining control parameters remains unaffected. Such changes in process, however, should be handled and documented according to the change control program.

4. PERSONNEL

Humans are the largest source of microbial contamination in aseptic processing areas (APA) for manufacturing operations; therefore, it is essential to minimize personnel intervention as a possible source of contamination within the processing area. Appropriate education and training on the concepts and practical procedures that personnel are required to perform should be provided. This will allow personnel to maintain a high skill level as well as improve their confidence and morale.

4.1. Personnel Training

1) SOPs for aseptic processing should be prepared, implemented, and monitored for adherence. The SOPs should contain concrete description of tasks that personnel are required to perform during aseptic processing.
2) Education and training programs for personnel working in the APA should be prepared and implemented. The levels of education and skill of each individual should be taken into account.
3) Education and training programs should include the items listed below at a minimum. These matters do not have to be implemented simultaneously, but need to be in place at the appropriate time and according to a written schedule. The extent and frequency of education and training should be adjusted for the skills, knowledge, and experience of individual personnel.
   A. Matters related to hygiene: Personnel working in the APA should not wear make-up or accessories that may damage the work jacket or gloves (e.g., rings with raised settings, earrings, or wrist watches).
   B. Matters related to aseptic technique
      (a) Personnel working in the APA should avoid unnecessary movement and any direct contact with critical surfaces.
      (b) Personnel should minimize movements and conversation that may generate airborne particles or create unacceptable turbulence in critical areas.
      (c) Personnel should avoid blocking or disrupting the airflow path directed to such items as unsealed containers, unprotected drug products, and packaging materials (e.g., rubber stoppers).
      (d) Personnel should not disrupt airflow directed at installations or equipment in critical areas that may come into contact with sterilized drug products and packaging materials.
      (e) Personnel should keep their gloves sanitized by frequent disinfection or other appropriate methods.
   C. Matters related to knowledge of basic microbiology

      Personnel should be educated about the following:
      (a) Characteristics of species that are likely to be encountered and their preferred growth conditions/locations and count.
      (b) Conditions leading to the proliferation or death of microorganisms as well as generation of endotoxins
      (c) Basic knowledge of the sterilization procedures to be used during manufacture
      (d) Environmental monitoring methods to be employed
   D. Matters related to gowning
   E. Matters related to aseptic processing technology appropriate for the personnel involved
   F. Matters related to the cleaning and disinfection of manufacturing equipment and manufacturing environment

      Personnel should be knowledgeable about the following:
      (a) Properties of cleaning agents and disinfectants as well as those of the materials to be cleaned or disinfected
      (b) Appropriate concentration to be prepared, method of preparation, and expiration date of cleaning agents and disinfectants to be used

(c) Points to consider when using cleaning agents and disinfectants

G. Potential hazards to humans if contaminated drug products are used

4) Personnel who enter the APA only occasionally (e.g., supervisors, QA/QC personnel, maintenance personnel) should be educated and trained on the following matters, as appropriate:
   A. Hygiene
   B. Basic microbiology
   C. Gowning procedures
   D. Acceptable behaviors and activities in the APA
5) Education and training items should be prepared in writing. The effectiveness of the education and training program related to the knowledge of aseptic processing should be evaluated.
6) All personnel engaging in aseptic processing operations should participate in a process simulation test at least once a year and should achieve predefined levels of performance.
7) Inexperienced personnel engaging in aseptic processing operations should participate in a process simulation test or some other similar simulated aseptic processing at least once prior to obtaining permission to engage in aseptic processing operations. This simulated aseptic processing may be performed in another processing area.
8) Inexperienced personnel who have obtained permission to enter the APA should be supervised by and receive on-the-job guidance from experienced personnel for a predefined period.
9) As a rule, only authorized personnel should enter the APA. When unauthorized personnel need to enter the APA for any reason, such as equipment repair, these personnel should obtain entry permission from the area supervisor and should be accompanied by appropriate personnel.

4.2. Personnel Health Management

1) Personnel who engage in aseptic processing operations should report any signs or symptoms, such as fever, skin damage, flu, or diarrhea that may affect operations in the APA to supervisory personnel.
2) When personnel report any abnormal physical conditions that may affect aseptic processing operations, the supervisor should not permit the entry of such personnel into the APA.

4.3. Microbiological Monitoring of Personnel

1) Personnel entering into certain APAs should be subject to a microbiological monitoring program specific to the area.
2) Microbiological testing of gloves and gown, whenever required, are performed by the agar contact plate method when personnel leave the APA.
3) Microbiological monitoring data for all personnel should be analyzed for trends at an appropriate frequency. Any personnel for whom undesirable trends develop should be re-educated and retrained.

5. Prevention of Contamination by Personnel

When any personnel develop undesirable microbiological monitoring trends for their gloves and/or gowns, such personnel should be promptly re-educated and retrained. If, after re-education and retraining, the follow-up data for these personnel do not indicate improvement, the supervisor should consider reassigning such personnel to other, non-APAs.

5.1. Gowning Requirements

1) Each employee should wear a gown as well as gloves and shoes designed especially for the APA before entering it.
2) A gowning room installed before the entrance of the APAs should be separated or partitioned from the degowning room to avoid cross-contamination. It is recommended that the gowning procedure be displayed by a sequence of pictures to foster understanding of gowning procedures, and that equipment such as a mirror to facilitate the checking of proper gowning be installed.
3) Headgear and gowns to be worn in the APA should be of a sufficient quality and characteristics as to function as intended (e.g., no shedding of particulate matter), taking the movement of personnel into consideration.
4) Personnel should be careful not to expose any body surface while in the APA.
5) Aseptic gowning standards, including frequency of gown change and sterilization conditions and methods, should be established and followed.
6) As a rule, protective gowns should be changed each time of entry into the APA. If a gown is reused without proper disinfection or sterilization, the acceptability of the reuse should be verified and the data recorded. Even if reuse is supported by data, a gown should not be worn in the aseptic area for more than one day or without being disinfected after sampling for microbiological testing.

5.2. Gown Control after Wearing

1) Personnel should adhere to appropriate documented procedures to prevent microbiological contamination of the APA.
2) Personnel should check to see if the gown fits appropriately and if the gown or gloves are torn or defective. If a gown or glove is found to be defective, it should be changed immediately, or another should be worn over the defective one.
3) Personnel should refrain from speaking after gowning and should not come into direct contact with the wall, floor, or sanitized surfaces unless necessary.
4) Appropriate personnel conduct and movement while in the APA should be specified in writing in order to restrict them to the necessary minimum.
5) After the initial gowning, gloves should be frequently sanitized, as appropriate, during aseptic operations.
6) Any personnel operating in supporting areas should not be permitted to enter critical areas or direct supporting areas or rooms without adequate training and proper gowning.
7) The number of personnel operating in the APA should be pre-designated for each shift of manufacturing operation, including the preparatory stage. Personnel handling sterile drug products, containers, or closures, or those engaging in operations in an environment where sterile drug products, containers, or closures are exposed, should be documented.

5.3. Gowning Training

1) Personnel should be trained on the hand washing, gowning, and degowning procedures required before entering and after leaving the APA. Supervisory personnel should regularly evaluate the operator's performance to confirm adherence to the established rules.
2) Personnel should be trained on appropriate gowning procedures to minimize contamination risk.
3) Gowning training effectiveness should be evaluated by particle monitoring or microbiological methods. Gowns should not be used in the APA without being disinfected after sampling for microbiological testing.
4) Supervisory personnel should inform the trainees of the training results.
5) Personnel should be trained on gown choice and adequate gowning procedures for entering the APA for inspection and/or equipment maintenance purposes after the shut down of aseptic conditions during manufacturing suspensions. The training program should include procedures for the entry of inspection, maintenance, or repair equipment into the aseptic area. When untrained personnel, including vendor engineers, enter the area, trained personnel should accompany them and instruct them on gowning and entry procedures.

6. Buildings and Facilities

6.1 Key Features of Facility Design

Clean areas for the manufacture of sterile drug products are classified into APAs (consisting of critical areas and direct supporting areas) and supporting areas. The facility design for the clean areas should meet the following general requirements:

1) Clean areas should be clearly separated from residential areas and unsanitary areas.
2) Clean areas should be clearly separated areas of a size appropriate for each processing activity.
3) Clean areas should be supplied with air filtered through an appropriate filter, e.g., a high efficiency particulate air (HEPA) filter, to maintain an acceptable level of air quality and pressure difference between areas or rooms for clean area operations.
4) Air pressure in clean areas should be maintained higher than that in adjacent rooms of lower cleanliness.
5) No doors, except for emergency exits, permitting direct access to the outside should be installed in clean areas.
6) Clean areas should be equipped with an appropriate environmental monitoring system for recording temperature, relative humidity, pressure differentials, etc.
7) Temperature and relative humidity in the clean areas should be controlled within a range compatible with the properties of the materials and products being handled there. Temperature and humidity should be also set at levels suitable for microbiological control.
8) Layout should be considered to minimize mingling of flows such as personnel, product, material, utensil, article, and waist material, and to facilitate their control.
9) Operating procedures and classified areas should be designed in such a way as to prevent mix-up of clean and dirty items and of sterilized and non-sterilized items.
10) Other suitable premises should be considered in the case that sensitized materials are handled.

11) Facilities should be designed to facilitate ease of cleaning, maintenance, and operations. Periodic maintenance should be performed to verify that the integrity of the design is being upheld.

6.2. Facility Design Features

Clean area design should meet the following floor layout and construction requirements:

1) Floors, walls, and ceilings should be constructed from materials that can be cleaned and withstand exposure to cleaning agents and disinfectants.
2) Ceilings should be effectively sealed.
3) The construction of irregular surfaces, windows, doors, horizontal surfaces, or ledges that may accumulate particles or disturb the airflow should be avoided.
4) Pipes, ducts, and other utilities in clean areas should be installed in such a manner as to ensure that their surfaces can be cleaned easily.
5) Adequate spaces or rooms for gowning, storage of gowns and protective apparel, disposal of used gowns and apparel, and hand washing should be provided.
6) Direct supporting areas should be separated from adjacent areas by an airlock. The areas between direct supporting areas and adjacent areas should be equipped with a pass-through room and/or pass-through box for the transfer of sterilized materials and equipment, or for the disinfection of materials and equipment which are difficult to sterilize.
7) Airflow pattern should be controlled in critical areas in order to maintain the sterility of the critical area surfaces as well as the drug products themselves.
8) The APA should be equipped with transparent (glass, etc.) windows or video cameras to facilitate observation from non-aseptic areas.
9) A substantial positive pressure differential should be maintained between areas of different air cleanliness.
10) Airlock doors should have a system to prevent the simultaneous opening of both sets of doors. In addition to mechanical or electrical interlocking systems, there should be visual or audible alarm systems in place to prevent simultaneous opening of the doors.
11) Environmental temperature and relative humidity should be controlled within specified limits and, wherever feasible, monitored continuously.
12) Layout of equipment in the APA should be designed to facilitate easy access by operators and maintenance personnel, minimizing exposure of open containers or products.
13) Installations and equipment that are not essential should be removed from critical areas.
14) Sinks and drains should not be installed in the APA.
15) Rooms in other supporting areas (Grade C or D) should be designed with a corridor and appropriately oriented so as not to permit the routine passage of personnel not directly engaged in the operations being conducted there.
16) Rooms for the weighing of raw materials or the washing of containers should be designed to close tightly and have appropriate airflow direction during use so as to not introduce contaminated air into adjacent rooms.
17) Rooms for the drying and sterilization of containers after washing should be used for these purposes exclusively. Clean containers that pose no risk of contamination may also be stored there.
18) Specifically defined areas should be considered when parenterals and other sterile drug products are manufactured in the same areas, and manufacturing facilities for drug solution

preparation, filling, and sealing operations should be used exclusively for those purposes in a closed system during manufacturing.

19) Rooms for the drug solution preparation, filling, and sealing of drug products and sterile API should be separate from those for non-sterile products or API, except for those posing no risk of contamination of sterile products and API.

20) Each of the drug solution preparation, filling, and sealing operations should be carried out in its own dedicated room that should be used exclusively for that individual purpose. However, this requirement does not apply to drug solution preparation and filling operations or drug solution preparation, filling, and sealing operations that are conducted continuously in the same rooms in a closed system. Non-parenteral sterile drug products may be filled or sealed in the same room in which the drug solution preparation is carried out if these operations are conducted in a closed system. Dedicated rooms may not be required for the drug solution preparation, filling, and sealing of radiopharmaceuticals.

7. Processing Areas of Sterile Drug Products

7.1. Classification of Manufacturing Areas by Air Cleanliness

Aseptic processing facilities for the manufacture of sterile drug products consist of clean areas that are controlled based on predefined airborne particle and microbiological standards. These areas are classified as "critical," "direct supporting," and "other supporting," depending on the nature of the operation.

Generally, the cleanliness of the air in clean areas is defined by the number of airborne particles 0.5 μm in diameter or larger per unit volume of air. The number of particles larger than 5 μm may be included as a parameter in the control program as appropriate.

Table 1 shows the air cleanliness requirements for each classified area.

Table 1. Classification of Clean Areas

Area		Air cleanliness*	Maximum allowable number of airborne particles ($/m^3$) Diameter: ≥ 0.5 μm	
			Count under non-operating conditions	Count under operating conditions
Aseptic processing area	Critical area	Grade A (ISO 5)	3,520	3,520
	Direct supporting area	Grade B (ISO 7)	3,520	352,000
Other supporting area		Grade C (ISO 8)	352,000	3,520,000
		Grade D	3,520,000	Dependent on process attributes

* The ISO class designation in parenthesis refers to the count during operation.

7.1.1. Critical Area (Grade A)

1) A critical area is one in which environmental conditions are designed to preserve the sterility of sterilized containers, components, and in-process materials, as well as the surfaces that come into direct contact with these things. Activities to be conducted in this area include the following:
   (A) The entire aseptic procedure, from sterile filtration up to closure (for sterile drug products to be manufactured by a series of aseptic procedures following filtration)
   (B) The entire aseptic procedure, from handling of the starting material to closure (for sterile drug products to be manufactured by a series of aseptic procedures starting with handling of sterile starting materials)
2) The per-cubic-meter particle content in critical areas should be controlled so as not to exceed more than 3,520 in the size range of 0.5 μm or larger under both operating and non-operating conditions. This level of air cleanliness is designated as Grade A, Class 100, or ISO-5, according to domestic and international standards on air quality.
3) The intervention of personnel into critical areas should be kept to a minimum.
4) Regular monitoring of the airborne particle and microorganism count should be performed by appropriate procedures at an adequate frequency at the sites where there is a greater potential risk of contaminating sterilized products so as to maintain the sterility of drug products.
5) Some powder filling operations can generate higher levels of airborne particles than the specified count. In this instance, background levels of airborne particles should be obtained for comparison by, for example, air sampling at different locations, or measuring air quality in the same room while no powder filling operation is going. By characterizing the true level of extrinsic particle contamination to which the product is exposed, the quality of air may be verified and checked against specifications.

7.1.2. Direct Supporting Area (Grade B)

1) The direct supporting area is defined as the background area of the critical area. It is the working area for personnel who operate machines installed in the critical area and for those who supervise the operation of machines. The area is also used as a route to transfer sterilized products, materials, and equipment to the critical area or to move sterilized products from the critical area. In the latter case, appropriate measures need to be taken to protect sterilized products or materials from direct exposure to the environment.
2) The per-cubic-meter particle content (particle size range: 0.5 μm and larger) in direct supporting areas should be controlled to not exceed 352,000 and 3,520 under operating and non-operating conditions, respectively. These levels of air cleanliness are designated as Grade B, Class 10,000, or ISO-7 (under standard operating conditions), according to domestic and international standards on air quality.
3) Regular monitoring of the airborne particle and microorganism count should be performed in direct supporting areas.

7.1.3. Other Supporting Areas (Grade C to D)

1) Other supporting areas function as zones in which non-sterile containers, components, and in-process materials are exposed to the environment, or where sterilization equipment and apparatuses are cleaned and stationed.
2) The specification for the airborne particle count in other supporting areas should depend upon the level of cleanliness required to prevent contamination and the nature of operations to be performed in the areas.
3) There are two other air cleanliness grades generally applied to the remaining supporting areas. One of the grades specifies that the per-cubic-meter particle content (particle size range: 0.5 μm and larger) should not exceed 3,520,000 and 352,000 under operating and non-operating conditions, respectively. These levels of cleanliness are designated as Grade C, Class 100,000, or ISO-8 (standard under conditions), according to domestic and international standards on air quality. The other grade specifies that the per-cubic-meter particle content (particle size range: 0.5 μm and larger) should not be more than 3,520,000 under non-operating conditions. This level of cleanliness is designated as Grade D.

7.2. Heating, Ventilation, and Air Conditioning System

A well-designed and controlled heating, ventilation, and air conditioning (HVAC) system is critical for the appropriate maintenance of air in clean areas. The integrity of the system should be insured with respect to not only operational activity-related short-term variations (i.e., the opening and closing of doors or operation of machinery), but also non- operational activity-related long-term variations (i.e., seasonal changes or deterioration of equipment and apparatuses over time). The HVAC system and its management program are comprised of the following basic elements: temperature, relative humidity, level of air cleanliness, air flow and exchange rates, unidirectional flow, pressure differential relative to adjacent rooms, and integrity of HEPA filter.

7.2.1. Temperature and Relative humidity

Temperature and relative humidity, which have a direct impact on the comfort of operators and the potential for microbial contamination, should be appropriately defined, controlled, monitored, and maintained.

7.2.2. Air

It is critical to secure proper airflow from areas of higher to those of lower cleanliness requirements in order to maintain the required environmental conditions of each clean area.

1) An adequate air pressure differential between the APAs and other supporting areas should be employed, controlled, and monitored.
2) A pressure differential between APAs and adjacent supporting areas should be substantial enough to prevent the reversal of defined pressure differential or airflow. For example, a pressure differential of at least 10 to 15 Pa should be maintained between adjacent rooms of differing cleanliness classifications. Likewise, an appropriate pressure differential should be maintained between other supporting areas of different cleanliness classifications.