Guidance on the Manufacture of Sterile Pharmaceutical Products by Aseptic Processing

Task Force

on

Sterile Pharmaceutical Products by Aseptic Processing

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Notice: This English version of the Guidance on Sterile Pharmaceutical Products Produced by Aseptic Processing is prepared for the convenience of users unfamiliar with the Japanese language. When and if any discrepancy arises between the Japanese original and its English translation, the former is authentic.

Table of Contents

1. Introduction

This guidance document describes the current basic concepts on sterility assurance and procedures for manufacturing and controlling sterile pharmaceutical products in order to advise manufacturers of sterile pharmaceutical products and regulatory personnel responsible for pharmaceutical inspections on sterility assurance.

This guidance is intended to be applied in the aseptic processing of parenteral drugs; however, its basic concepts may also be useful when manufacturing ophthalmic solutions and other sterile pharmaceutical 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 The concepts and descriptions contained in this guidance may be superseded by other processes or procedures of manufacture that are justifiably comparable or more stringent (except for the Ministerial Ordinance, "Regulations for Manufacturing Control and Quality Control of Medicinal Products and Quasi-Medicinal Products" ["GMP regulations," Ordinance No. 179, 2004], and other regulatory requirements, notifications, and issues), as long as the quality of pharmaceutical products can be ensured.

2. Glossary

2.1 **Air lock:** A small room that is generally composed of interlocked doors, constructed to maintain air pressure control between adjoining rooms. 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.

2.2 **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** **Alert level:** Established criteria of microbial or airborne particle level (and microbial species if necessary) giving early warning of potential drift from normal conditions.

2.**5** **Aseptic filling:** A Part of aseptic processing where sterilized products are filled and/or packaged into sterile containers and closed under Grade A area.

2.6 **Aseptic processing:** A method of producing sterile products in which sterile bulk product or sterile raw materials are compounded and filled into sterile containers in a controlled environment, in which the air supply, materials, equipment and personnel are regulated to control microbial and particulate contamination to acceptable levels.

2.7 **Aseptic processing area (APA):** Controlled environments, in which the air supply, materials,

equipment and personnel are regulated to control microbial and particulate number to acceptable levels. APA is consisted of “critical (processing) area” and “direct support area.”

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

2.9 Bioburden: Population of viable microorganisms which may be present in non-sterile drugs or materials including intermediate products and raw materials.

2.10 Biological indicator (BI): 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.

2.11 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

2.12 Chemical indicator (CI): 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.

2.13 Clean area: An area maintained and controlled to prevent contamination of pharmaceutical products with microorganisms or foreign substances, in compliance with defined particle and microbiological cleanliness standards. For the purposes of this document, this term is synonymous with manufacturing area for aseptic products.

2.14 Colony forming unit (CFU): Visible growth of microorganisms arising from a single cell or multiple cells.

2.15 Critical area: A limited processing area where sterilized containers, raw materials, intermediate products or the surface of equipment that comes into contact with sterilized product is exposed to environment. This area is also known as the “critical processing area.” The level of environmental cleanliness of this area is commonly referred to as Grade A.

2.16 Critical processing: A process that can affect one or more critical quality attributes of a pharmaceutical product.

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

2.18 Decontamination: A process that reduces or removes contaminating substances to a defined acceptance level using a reproducible method.

2.19 Design qualification (DQ): Documented verification that the proposed design of the facilities, equipment, or systems is suitable for the intended purpose.

2.20 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.

2.21 Disinfection: A process by which environmental or equipment bioburden is reduced to a safe level or eliminated.

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

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

2.24 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 pharmaceutical 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.

2.25 Heating ventilation and air condition (HVAC) system: An air handling system including heating, ventilation, and air conditioning.

2.26 High efficiency particulate air (HEPA) filter: Air filters designed to retain particulates of larger than a certain size with defined efficiency. The filter retaines particles of ≥ 0.3 μm size with a minimum efficiency of 99.97%.

2.27 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.

2.28 Installation qualification (IQ): Documented verification that the equipment or systems, as installed or modified, comply with the approved design, the manufacturer’s recommendations and/or user requirements.

2.29 Integrity test for containers: Test for confirming container’s closure integrity as a part of stability testing for sterile products until the use.

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

2.31 Isolator: A sealed and sterilized enclosure capable of preventing ingress of contaminants by means of total physical separation of enclosure to the surrounding exterior environment, An isolator’s air supply is filtered using HEPA or ULPA grade filters.

2.32 Gas filter: Hydrophobic filters equipped in compressed air pipe lines for the porpose of removing microorganisms and particulates from gases.

2.33 Leak test: A test performed to verify that air leak from equipment/ devices and the container closure system that require to maintain sealing performance remains within the specified limits**.**

2.34 Material safety data sheet (MSDS): 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 under "Pollutant Release and Transfer Register" for all aspects of commerce involving chemicals designated in the ordinance as Class I Designated Chemical Substances, Class II Designated Chemical Substances and products containing these substances.

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

2.36 Operational qualification (OQ): Documented verification that the equipment or systems, as installed or modified, perform as intended throughout the anticipated operating ranges.

2.37 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.

2.38 Performance qualification (PQ): Documented verification that the equipment and ancillary systems, as when operating together, can perform effectively and reproducibly based on the approved process method and specifications.

2.39 Process parameter: Specified value for a process variable.

2.40 Process simulation test or 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.

2.41 Pure steam: Saturated steam that is generally produced using purified water or water of better quality and will then be condensed into such high grades of water that meet the criteria for water for injection under Pharmacopoeia.

2.42 Quality system: Organizational structure, procedures, processes and resources needed to implement quality management.

2.43 Restricted Access Barrier System (RABS): An integrated system that possesses aseptic processing areas (critical areas) and is composed of some critical elements such as rigid wall enclosure (often equipped with gloves), unidirectional airflow least- to through HEPA filters and appropriate operation procedures.

2.44 Sanitation/sanitization: Hygienic means of facilities and equipment by disinfection, cleaning,

hot waters, etc.

2.45 Standard operating procedure (SOP): 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 Standard Operating Procedures (SOPs) may be used to supplement product-specific master and batch production documentation.

2.46 Sterile: Free from viable microorganisms.

2.47 Sterility assurance level (SAL): Probability of a single viable microorganism being present in a product unit after exposure to the proper sterilization process, expressed as 10^{-n}.

2.48 Sterilization: A process that destroys or eliminates all microorganisms which is used to render a product free from viable microorganisms.

2.49 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 under specified conditions. The nominal pore size of the filters ranges from 0.20 to 0.22 μm.

2.50 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. Typically, the sterility assurance level should be less than 10^{-6}.

2.51 Unidirectional airflow: Air flow which has a singular direction of flow and may contain uniform velocities of air flow along parallel flow lines.

2.52 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.

3. Quality System

The quality system for aseptic manufacturing of sterile pharmaceutical products is structured to satisfy the requirements for the establishment, documentation, implementation, and maintenance of an efficient and adequate quality control system in compliance with Sections 1 (General Rules) and 3 (Manufacturing Control and Quality Control of Sterile Pharmaceutical Products) of Chapter 2 of the current GMP regulations.

3.1 General Requirements

1. General

The written quality system should comprise an organizational structure and description of

operational procedures, manufacturing processes, resources used, and activities necessary to ensure compliance with the requirements for aseptic processing of sterile pharmaceutical products stipulated in this guidance document.

All quality control-related activities to be undertaken, including sterility assurance-related activities, should be identified and documented in detail. Manufacturers of pharmaceutical products under aseptic conditions are also required to establish and implement an adequate quality system by setting up quality control standards suitable for the prevention of microbial product contamination during processing. This quality system should include an investigation system for identifying deficiencies in sterilization procedures and assessing abnormalities or deviations in control parameters from the standards, as well as a verification system for ensuring the acceptability of corrective and preventive measures taken and whether or not the outcome of these measures was achieved.

2. Scope of application

This guidance is applicable to the quality system governing all processes in sterile pharmaceutical product manufacturing at facilities where pharmaceutical products are manufactured under aseptic conditions. In practice, the scope of application includes environmental control, control of laboratory testing of sterile pharmaceutical products, quality control of aseptic processing, validation, and systematized control of manufacturing processes and product quality such as documentation and change control.

3. Document control

The following documents should be prepared, used for fulfilling requirements stipulated in each provision of this document, and archived to ensure the sterility of sterilized pharmaceutical products: documents on initial, periodic and change validation; standard operating procedures (SOPs); area maps with cleanliness levels; movement diagrams of raw materials, personnel, intermediate products, and finished products; equipment and instrument layout charts; instructions; records of data; deviation control records; change control records; out-of-specification (OOS) test results; calibration records; environmental monitoring records; log books; and computer system data (e.g. records stored on electronic media).

4. Risk management

The concept and procedures for risk management should be included in the quality system, and contamination preventive measures should be implemented to minimize risks of contaminating pharmaceutical products with microorganisms, endotoxins, and foreign matters. The risk management system should be based on risk assessment procedures for analyzing and evaluating factors affecting product sterility and contamination with endotoxins and foreign matters as well as based on verification of risk control procedures for demonstrating the

reliability and validity of risk avoidance procedures.

5. Qualification of aseptic processing environment

   Environmental parameters of the aseptic processing area should be identified and verified for qualification. Based on qualification assessment results, a program for HVAC system maintenance and environmental monitoring should be established and implemented.

6. Qualification of aseptic processing equipment and facilities

   Equipment and instruments used for the manufacture of sterile pharmaceutical products in the aseptic processing area as well as other equipment and facilities that may affect aseptic processing should be evaluated for qualification. Based on qualification assessment results, a program for maintaining the equipment and facilities should be established.

7. Prospective validation and periodic review of process control

   Process validation that simulates all processes and activities related to sterilization of pharmaceutical products should be conducted. Such processes and activities are required to achieve commercial sterility of pharmaceutical products based on scientific evidence-based designs and operations. A process control program should also be established and validated.

8. Periodic revalidation

   Periodic revalidation should include a process simulation program and periodic valuation of sterilization processes that may affect the sterility of pharmaceutical products.

9. Time limitation for aseptic manufacturing operations

   Manufacturing processes of sterile pharmaceutical products from the preparation of drug solution to filtration and sterilization should be conducted as quickly as possible. The maximum allowable time from filtration, storage, and filling to sealing should be established by taking into account the product composition, manufacturing processes, and storage conditions as well as risks inherent to these processes.

10. Cleaning and disinfection of facilities and equipment

    A program for cleaning and disinfecting facilities and equipment should be established taking into account the potential development of drug-resistant microorganisms. The program should contain procedures for screening and classifying bacterial isolates in each manufacturing environment.

11. Pest control

    An appropriate pest control program should be directed to aseptic manufacturing facilities to prevent contamination of sterile pharmaceutical products with insects and other vermin.

12. Flow of raw materials

    Flow diagrams of raw materials, parts, and other articles necessary for processing products

into the aseptic processing area should be established and, as the situation may require, appropriate disinfection and sterilization procedures should be implemented. Appropriate measures should be takento prevent microbial invasion into the working area during the transfer of raw materials and other materials.

13. Gowning and flow of personnel

    Appropriate procedures should be practiced to prevent microbial invasion into the aseptic processing area during the entry or exit of personnel. Gowning procedures and flow of personnel should be standardized.

14. Change control

    Changes in standard procedures should be confirmed to have no negative impact on the sterility of pharmaceutical products based on scientific evidence. Changes implemented should be evaluated by applicable qualification and validation procedures, and, wherever possible, control parameters should be established to control risks inherent to such changes based on risk assessment results.

15. Calibration

    A calibration program including calibration frequency and accuracy requirements should be established and implemented to calibrate analytical equipment used in quality testing and measuring, inspection, and control devices used in the manufacturing process.

3.2 Routine Monitoring and Control

1. An environmental monitoring program should be established based on results of environmental tests performed to evaluate the qualification of the aseptic processing area.
2. Cleaning and disinfection of the aseptic processing area should be conducted periodically or as-needed to verify that the area meets predefined environmental control specifications.
3. A maintenance program should be established and implemented based on results of qualification and validation tests.
4. A process control program verified by validation experiments should be implemented.
5. Revalidation should be carried out at predetermined intervals.

3.3 Validation

The manufacture of sterile pharmaceutical products by aseptic processing can be achieved by harmonized application of hardware such as well-designed facilities and equipment and software, such as SOPs and adequate control systems and programs. In the qualification of an aseptic processing environment and manufacturing equipment and process validation, not only the safety,

efficacy, and uniformity of the manufacturing process but also the maintenance of required cleanliness levels of the sterilization procedure, filling and other aseptic processes should be ensured. In addition, sterility of the processing environment as well as scientific estimation of contamination risks for commercial production facilities and equipment and commercial manufacturing processes should be ensured to help avoid product contamination. Validation of sterilization procedures should include validation of sterility of raw and other materials supplied by external sources and maintenance of sterility during transport.

The fundamental requirement for manufacturing process control is to control the process based on validated operating procedures and process control parameters. When attempting to streamline the manufacturing process, the proposed alterations, which may include omission of one or more process parameters or shortening of process duration, should be assessed for possible risks, and proposed changes should be justified by scientific rationale and revalidated as appropriate.

4. Personnel

Humans are the largest source of microbial contamination in aseptic processing areas (“APAs”) for manufacturing operations. It is essential to minimize personnel intervention as a possible source of contamination of pharmaceutical products to eliminate the source of contamination within the APA for manufacturing sterile pharmaceutical products. Appropriate education and training on the concepts and practical procedures that factory personnel are required to perform should be provided to maintain high skill levels and improve confidence and morale.

If instruments such as isolators and blow-fill-seals are considered necessary in lowering the potential for human-related microbial contamination to occur, the importance of personnel education and training including those on characteristics and operating procedures of instruments should be taken into account for adequate operation, maintenance, and control of the instruments.

4.1 Personnel Training

1. SOPs for aseptic processing should be developed and in place. The SOPs should contain detailed descriptions of tasks that personnel are required to perform during aseptic processing.
2. An education and training program should be prepared and implemented for personnel engaged in the manufacture of sterile pharmaceutical products in the APA. The level of training should be dependent on the knowledge and skills of individual personnel.
3. At least the following matters should be included in the education and training program on aseptic processing. While these matters need not be addressed simultaneously, they should be practiced without fail in accordance with a pre-established training schedule. The contents of the program and frequency of training should be individualized according to the scope of work

or assignment, skills, knowledge, and experience of personnel.

(1) Hygiene

- Personnel engaged in operations in the APA for manufacturing sterile pharmaceutical products should not wear make-up or accessories (e.g. rings with raised settings, earrings, wrist watches) that may damage work gowns, jackets, gloves, caps, or masks.

(2) Aseptic techniques

- Personnel working in the APA should avoid unnecessary movements and direct contact with critical surfaces.
- Personnel should minimize movement and conversation in the APA that may generate airborne particles or create unacceptable turbulence in critical areas.
- Personnel should avoid blocking or disrupting the airflow path directed to unsealed containers, unprotected pharmaceutical products, and packaging materials (e.g. rubber closures).
- Personnel should not disrupt airflow directed at the surface of sterilized materials or pharmaceutical products placed in critical areas.
- Personnel should keep their gloves sanitized by frequent disinfection or other appropriate procedures.

(3) Knowledge of basic microbiology and skills of microbiological testing

- Understanding the type, properties, and detection methods of microbial species that are likely to be encountered during manufacture
- Understanding conditions leading to the proliferation or death of microorganisms as well as generation of endotoxins
- Understanding basic knowledge and skills of sterilization procedures to be used
- Understanding environmental monitoring methods to be employed

(4) Gowning procedures

- Personnel should be trained in proper hand washing, gowning, and degowning procedures required before entering and after leaving the APA. The supervisor should periodically evaluate their performance to confirm their adherence to established rules on gowning, etc.
- Personnel should be trained on appropriate gowning procedures to minimize contamination risks in the APA.
- Training effectiveness on gowning procedures should be evaluated by a particle

monitoring and microbiological tests. Gowns used during microbiological testing should not be reused in the APA unless disinfected after testing.

- The supervisor should communicate gowning training results to personnel trained.
- Training of gowning procedures should be conducted in an equipment inspection and maintenance situation or APA entry situation after deregulating aseptic conditions while production is suspended. The training program should also include advice on handling instruments to be brought into the APA. When untrained personnel, including vendor engineers, enter the area, trained personnel should accompany them to advise on procedures for adequate gowning and handling of instruments brought in.

(5) Aseptic processing technology necessary for personnel in manufacturing sterile pharmaceutical products

(6) Cleaning and disinfection of manufacturing environment and equipment

- Properties of cleaning agents and disinfectants as well as materials to be cleaned or disinfected
- Concentrations, method of preparation, and expiration date of cleaning agents and disinfectants used
- Points to consider on the use of cleaning agents and disinfectants

(7) Potential hazards that may affect humans if contaminated pharmaceutical products are administered

4. Personnel (e.g. manufacturing supervisors, QA/QC personnel, maintenance personnel) who may occasionally enter the APA should be educated and trained on the following matters, as appropriate:

(1) Hygiene

(2) Microbiology

(3) Gowning procedures

(4) Acceptable behaviors and activities in the APA

5. Education and training topics should be identified in writing, and educational effectiveness of the training program in increasing knowledge and skills of aseptic processing should be evaluated.

6. All personnel engaged in aseptic processing operations should participate in a process simulation test at least once a year, as a rule, and should achieve a predefined level of performance.

7. Personnel with no experience in aseptic processing operations should participate in a process

simulation test or other similar aseptic processing operations at least once, as a rule, prior to obtaining permission to engage in operations in the APA. Training of “other similar aseptic processing operations” may be conducted in a non-APA (e.g. training environment).

8. Inexperienced personnel who have been allowed to enter the APA should be supervised by experienced personnel for a predefined period and receive on-the-job guidance and subsequent evaluation of performance.
9. As a rule, entry into the APA should be restricted to personnel who have obtained prior permission to enter the area. When personnel need to enter the area for any reason, such as equipment repair, those personnel should obtain entry permission from the supervisor of the area and be accompanied by authorized personnel throughout their stay in the area.

4.2 Personnel Health Management

1. Personnel should report any clinical signs or symptoms to the supervisory personnel prior to engagement in operations if affected with fever, skin damage, flu, or diarrhea that may affect aseptic processing operations in the APA.
2. The supervisor should not permit the entry of the personnel into the APA when informed of physical abnormalities that may affect aseptic processing operations.

4.3 Personnel Management

1. Personnel who engage in operations in the APA should be subject to personnel management in accordance with an APA-specific microbiological monitoring program.
2. Microbiological testing should be performed immediately before leaving the APA, if gowns and other clothing may contact agar during testing.
3. Microbiological monitoring data obtained from individual personnel should be analyzed to determine a trend of contamination-risk increase for individual personnel at an appropriate frequency. Personnel who show an undesirable trend in contamination should be educated and trained repeatedly until acceptable data are obtained.

5. Prevention of Contamination by Personnel

If any personnel show unacceptable microbiological data obtained by monitoring gowns and other clothing, such personnel should be educated and trained again at the earliest possible occasion. If re-education and retraining fail to improve microbiological contamination rate, the supervisor should consider the reassignment of such personnel to non-APAs.

5.1 Gowning Requirements

1. Personnel should wear an APA-specific gown and other stuff including shoes before entering the processing areas for sterile pharmaceutical products. Basic garments include a sterilized or disinfected gown, shoes, overshoes, gloves, goggles, and mask. The use of clean undergarments and dual layer gloves should be considered, as the situation may require.
2. A gowning room located 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 in the gowning room of the APA used for manufacturing sterile pharmaceutical products by a sequence of pictures to aid in understanding of gowning procedures and that a mirror be installed to facilitate checking of proper gowning.
3. Gowns and other stuff to be worn in the APA for sterile pharmaceutical products should be highly functional and suitable for working in the APA and free of generating or discharging particulate matter into the environment.
4. Personnel entering the APA should not expose any body surfaces to the environment while working in the APA.
5. Cleanliness of gowns and other stuff should be managed by internal control standards, including frequency of change and sterilization methods and conditions, established and implemented to maintain the cleanliness as required.
6. Sterile gowns and other stuff worn in the APA should be changed each time entering the area, as a rule. If gowns and other stuff are permitted by the internal control standards to be reused without disinfection or sterilization, the validity of the reuse should be verified with experimental data. Even if the reuse is supported by data, gowns and other stuff worn for more than one day or worn during microbiological sampling should not be reused without disinfection.
7. It is recommended that personnel wear dedicated undergarments (e.g. layered clothing for complete skin coverage) or over gowns.

5.2 Requirements for Aseptic Processing

1. Personnel should adhere to SOPs for the prevention of microbiological contamination of the APA.
2. Personnel should check to see if the gowns and other stuff fit properly and are not torn or defective. If a gown or gloves are found to be defective, necessary counteractions such as changing or layering of new garments over the defective ones should be immediately taken.
3. Personnel should refrain from speaking after gowning and should avoid direct contact with the

wall, floor, or sanitized surfaces unless necessary.

4. Applicable SOPs should include a provision that restricts unnecessary personnel movement, such as touching of materials and walls, while staying in the APA.
5. Personnel operating in indirect support areas should not be permitted to enter critical or direct support areas or rooms if they do not change gown and other stuff or are not adequately trained on proper gowning procedures.
6. The number of personnel operating in the APA should be set at a minimum for each shift of manufacturing operations, including the preparatory stage. Personnel handling sterile pharmaceutical products, containers, or closures and those engaging in operations in an environment where sterile pharmaceutical products, containers, or closures are exposed should be identified and recorded.

6. Buildings and Facilities

6.1 Key Features of Facility Design

Clean areas for the manufacture of sterile pharmaceutical products are classified into APAs (comprising critical and direct support areas) and indirect support areas. These clean areas should be designed by taking into account the following matters as general requirements:

1. Clean areas should be clearly separated from rest rooms, and eating areas.
2. Clean areas should be well-separated for intended purposes from other processing operations within a facility, and should have sufficient space to allow proper conduct of all manufacturing operations that are to be done within them.
3. Clean areas should be designed to achieve efficient flow and control of materials, products, and personnel within the areas. The location of equipment in the areas should also be carefully planned to minimize crossing of personnel, products, and materials flows.
4. Material handling procedures or fixed depots should be efficient in preventing a mix-up between clean and dirty or sterilized and non-sterilized apparatuses and utensils.
5. Facilities should be designed to facilitate ease of cleaning, maintenance, and operations and periodically inspected to verify that the facilities are maintained as originally designed. Particular consideration should be given to seals and packing of interior materials such as doors, walls, ceilings in order to keep processing rooms tightly closed. Insulation materials to prevent dew drops should be maintained to work well.
6. Ceilings should be effectively sealed.
7. Installation of irregular surfaces and horizontal frames around windows and doors should be avoided to reduce collection of particulate matter and microorganisms and to avoid

disturbance of airflow. If such designs are unavoidable, their structures should be suitable for easy cleaning. Sliding doors may be undesirable for this reason.

8. Adequate space should be provided for gowning, storage of gowns, and disposal of used gowns and other materials.

9. Transparent (e.g. glass) windows or video cameras should be installed in the APA to facilitate observation and supervision from non-aseptic areas.

10. Layout of equipment in the APA should be designed to minimize environmental exposure of open containers or finished products and facilitate easy access of personnel to these items during processing or quipment maintenance.

11. Equipment not essential for processing in the critical area should be installed in non-critical areas.

12. Corridors should be adequately distributed along working areas in indirect support areas (Grade C or D) in order to prevent those areas from being used for routine passage of personnel not directly engaged in processing in the areas.

13. When parenteral and other sterile drug products are manufactured simultaneously in the same room, manufacturing equipment for preparation, filling, and sealing of drug products should be dedicated and should be closed system for those operation. If any part of the equipment structurally is kept open, appropriate measures and activities should be implemented to prevent contamination.

14. The working areas for preparation, filling, and sealing of sterile drug products and sterile API should be separated from the areas for processing non-sterile drug and non-sterile API. The separation is not necessary if there is virtually no risk of contamination of products processed in the working areas.

15. Facilities should be structurally designed to be efficient in preventing or minimizing risks of cross contamination if used for processing highly pharmacologically active substances, pathogenic substances, highly toxic substances, radioactive substances, live viruses, or bacteria.

16. Walls, floors, and ceilings should be easily cleanable and durable against cleaning agents and disinfectants.

17. Drains and sinks should be prohibited in the APA. If drains are placed in Grade C areas in indirect support areas, drains should be fitted with traps or water seals parts which are easy to clean and disinfect to prevent contamination by back-flow. If floor trenches are located, they should be shallow to facilitate cleaning.

18. Piping, air ducts, and other utilities in clean areas should be installed so that they do not create

recess and surfaces which are difficult to clean.

19. 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. The pressure difference should be monitored to maintain as specified.

20. Temperature and relative humidity in clean areas should be controlled within ranges compatible with the properties of materials and products being handled in the areas and also set at levels suitable for microbiological control.

21. Environmental temperature and relative humidity should be controlled within specified limits and, wherever feasible, monitored continuously.

22. Air pressure in clean areas should be maintained higher relative to adjacent lower cleanliness areas through doors, except for containment philosophy facilities for handling potent substances.

23. Airflow patterns in critical areas should be controlled to maintain sterility of critical surfaces and products.

24. Direct support areas should be separated from adjacent areas by airlocks. Spaces located between direct support areas and adjacent areas should be equipped with pass-through rooms and/or pass-through boxes for transfer of sterilized materials. Airlocks should also allow for proper disinfections or decontamination of wrapped goods, tools and other materials used in the APA when necessary..

25. Airlock doors should be equipped with a system that prevents simultaneous opening of both sets of doors (e.g. mechanical and electrical interlocking systems and visual and audible alarm systems).

26. The gowning room should be equipped with an airlock system and physically portioned into gowning and degowning areas. Air particulate cleanliness in the gowning room should be maintained at the same grade as the area (at rest) into which it leads. In order to reduce rapidly numbers of particles accompanied with gowning activity, volume and/or air change rate of the room should be adequately considered. Supply air at a relatively high position and exhaust air at a lower position in the room are desirable. The air cleanliness of the pass box should be specified according to the intended the purpose of use.

27. The use of separate changing rooms entering and leaving clean areas especially in the direct supporting areas is desirable. As an alternative measure, it is acceptable to stagger time of entry and exit.

28. Gowning rooms should be adequately located depending on cleanliness of the working rooms. Even if the cleanliness level is the same among areas, additional gowning rooms should preferably be set up depending on potential risks of contamination if there are risks of cross

contamination of raw materials and pharmaceutical products.

29. Rooms for weighing raw materials or washing containers should be carefully designed to secure seal integrity of doors and maintain appropriate airflow so as to not introduce contaminated air into adjacent rooms.

7. Processing Areas for Sterile Pharmaceutical Products

7.1 Classification of Manufacturing Areas by Air Cleanliness

Facilities for processing sterile pharmaceutical products comprise clean areas controlled based on predefined airborne particle and microbiological standards. The areas are classified as critical, direct support, and indirect support areas depending on the nature of the operation to be conducted.

Generally, the cleanliness of air in processing areas is defined by the number of airborne particles ≥ 0.5 μm in diameter per unit volume of air. The number of particles ≥ 5 μm in diameter may serve as a reliable parameter for early detection of environmental deterioration, if regularly monitored and evaluated by linear trend analysis. Table 1 shows the air cleanliness requirements for classified areas.

Table 1. Categories of Clean Areas

Area		Air cleanliness Note 1)	Maximum allowable number of airborne particles ($/m^3$)			
			Count under non-operating conditions		Count under operating conditions	
			≥ 0.5 μm	≥ 5.0 μm	≥ 0.5 μm	≥ 5.0 μm
Aseptic processing area	Critical area	Grade A (ISO 5)	3,520	20	3,520	20
	Direct support area	Grade B (ISO 7)	3,520	29	352,000	2,900
Indirect support area		Grade C (ISO 8)	352,000	2,900	3,520,000	29,000
		Grade D	3,520,000	29,000	Dependent on process attributes Note 2)	

Note 1) The ISO class designation in parenthesis refers to the count during operation.

Note 2) There are cases where maximum allowable number may not be specified.

7.1.1 Critical Area (Grade A)

1. The critical area is a processing area where sterilized products and materials as well as their surfaces are directly exposed to the environment. The environmental conditions should be specified to be suitable for the virtual elimination of contamination risks and preservation of the sterility of products. The following processes are conducted in this area: sterilization activities (e.g. sterile connections, addition of sterile materials) prior to filling, sterile filling, and sterile closure.
2. The per-cubic-meter content of particles ≥ 0.5 μm in diameter in the critical area should be controlled to be below 3,520 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 the critical area should always be kept to a minimum.
4. The count of airborne particles and microorganisms should be regularly monitored by appropriate procedures at sites which are critical for ensuring sterility of pharmaceutical products.

   It is recommended that airborne particles be continuously counted throughout aseptic processing, including during critical preparatory steps such as assembly of sterile parts that may contact pharmaceutical products. The location of monitoring should preferably be as close (≤ 30 cm) as the working place.

   The frequency and method of microbiological monitoring should be carefully selected in order not to break sterility of products by the monitoring.
5. Powder filling operations may generate higher counts of airborne particles than the specifications. If such a deviation occurs, the count of airborne particles should be obtained by, for example, sampling air at different locations or monitoring the count in the same room while no powder filling operation is going, and causes of the deviation should be identified to maintain air quality in the room at a required level.

7.1.2 Direct Support Area (Grade B)

1. The direct support area is defined as a background area of the critical area when aseptic processing is conducted using an open clean booth or restricted access barrier system (RABS). The direct support area is a working area for personnel who operate machines installed in the critical area and for those who supervise the operation of machines. The direct support area also serves as a route for the transfer of sterilized products, materials, and equipment to the critical area or for moving sterilized products from the critical area. In the latter case, appropriate measures need to be implemented to protect sterilized products or materials from

direct exposure to the environment.

2. The per-cubic-meter count of particles (diameter: ≥ 0.5 μm) in the direct support area should be controlled below 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. The count of airborne particles and microorganisms should be regularly monitored by appropriate procedures in the direct support area. The frequency and method of monitoring should be carefully selected based on evaluation results of product contamination risks in the critical area.

7.1.3 Indirect Support Areas (Grade C or D)

1. The indirect support area is an area used for processing materials and products prior to sterilization processes and hence materials and products are directly exposed to the environment. Example indirect support areas include an area for preparing drug solution prior to sterilization and an area for washing and cleaning sterilization equipment and apparatuses.
2. The cleanliness of the indirect support area needs to be controlled by establishing specifications for acceptable airborne particle count by taking into account the required level of contamination control and type of works performed in the area.
3. Air cleanliness of the indirect support area may be either of the following two grades. One of the grades specifies that the per-cubic-meter particle content (diameter: ≥ 0.5 μm) 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 operating conditions) according to domestic and international standards on air quality. The other grade specifies that the per-cubic-meter particle content (diameter: ≥ 0.5 μm) should not exceed 3,520,000 under non-operating conditions. This level of cleanliness is designated as Grade D.
4. Weighing and preparation processes should preferably be conducted in Grade C or cleaner areas. If powder handling might elevate the airborne particle count above the specification, air quality should be maintained below the specification by accurately determining the particle count that may cause contamination in the area, and for the determination, air should be sampled, for example, at multiple locations and/or under powder-free conditions.

7.2 Heating, Ventilating and Air Conditioning System

Air in clean areas needs to be maintained at appropriate levels by designing, instituting, and managing a suitable heating, ventilation, and air conditioning (HVAC) system. The integrity of the system should be ensured with respect to not only temporal variations due to operational activities, such as door opening and closing and facility equipment operation, but also sustained variations due to non-operational activities, such as seasonal changes in outdoor conditions 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, air flow volume, air exchange rate, unidirection of air flow, pressure difference relative to adjacent rooms, integrity of HEPA filter, airborne particle count, and microbacterial count.

7.2.1 Temperature and Relative Humidity

Temperature and relative humidity have a direct impact on the comfort of personnel and potential for microbial contamination in processing areas; therefore, these environmental parameters should be appropriately defined, controlled, monitored, and maintained at appropriate levels throughout processing.

7.2.2 Air

It is critical to secure constant airflow from an area of higher cleanliness level to an area of lower cleanliness level in order to maintain required environmental conditions of clean areas.

1. Pressure difference between the APA and indirect support areas should be adequately defined, monitored, and controlled.
2. Air locks should be established between the APA and indirect support areas and pressure difference between these areas should be maintained at a level sufficient to prevent the reversal of defined pressure difference or airflow. For example, a desired pressure difference between areas, when both closed, should be at least 10 to 15 Pa. The air lock design should meet requirements defined in Item 26 (gowning room) in Article 6.1. Likewise, an appropriate pressure difference should be established and maintained between indirect support areas of different cleanliness levels.
3. Wherever pressure difference is an essential part of sterility assurance, it is recommended to continuously monitor pressure difference between areas and install an alarm system to enable prompt detection of abnormal pressure differences.
4. Airflow in the critical area (Grade A) should be unidirectional and supplied at velocity and

uniformity sufficient to swiftly remove airborne particles away from the critical area. Airflow should also be supplied with sufficient care so as not to create reverse currents from adjacent areas (direct support areas, Grade B) into the critical area to prevent contamination. When conventional clean benches and RABS are used, the recommended mean flow rate is 0.45 m/sec ± 20%. Lower flow rate may be necessary depending on the type or usage of isolator system.

5. The airflow requirements stated in the preceding Item 5) should be verified by appropriate method of validation by smoke test or other qualification tests at the installation of airflow equipment. Similar validation is also necessary when airflow patterns are changed or suspected of being changed.
6. Changes in flow velocity can alter flow direction when airflow is specified to be unidirectional. The velocity should be confirmed to be constant at a predetermined level by monitoring the velocity of airflow from HEPA filters at time intervals specified in the program.
7. An appropriate air change rate should be established by evaluating the potential of product contamination for individual processing areas and gowning rooms in the APA to maintain air cleanliness at specified levels. The generally recommended air change rate is 30 times per hour in the direct support area and 20 times per hour in Grade C work rooms among indirect support areas. These change rates should be monitored at regular intervals to verify that the rates are continuously maintained as specified. Air current should be controlled not to ascend to prevent deterioration of work environment due to dust and bacteria stirred up from the floor. The most common method of securing downward current is to install supply vents close to the ceiling and exhaust vents close to the floor. Similar considerations on ventilation are applicable to indirect support areas, although the rigidity of specifications depends on potential risks of contamination with microorganisms and foreign matter.
8. The cleanliness of the work room must be promptly returned to the non-operating level after completion of processing and workers leave the room. In the direct support area, airborne particle count should preferably be returned to the non-operating count in 15 to 20 minutes.
9. Intended differential pressure and airflow patterns during processing should be specified and documented and then validated to be suitable and appropriate for commercial manufacture. The impact of turbulence created by the movement of personnel on the cleanliness of the manufacturing environment should be evaluated, and evaluation results should be reflected in relevant SOPs.

7.3 Integrity of HEPA Filters

7.3.1 Certification of Quality

1. HEPA filters should be accompanied by vendor's certificate of quality verifying that the filter is capable of eliminating at least 99.97% of particles ≥ 0.3 μm in diameter.
2. Leak test of HEPA filters to be used in critical areas (Grade A) and direct supporting areas (Grade B) should be performed by using appropriate leak testing aerosols, e.g. poly-alpha-olefin (PAO). When alternate aerosols are used, such aerosols should be used after confirming that they do not promote microbial growth.

7.3.2 Testing of HEPA Filters at Installation and at Regular Intervals

1. HEPA filters should be tested for leaks at installation and thereafter at suitable time intervals. The procedure and frequency of testing should be tailored to the environment, where the filters are installed, and their intended purpose of use. The integrity of HEPA filters in the critical area and direct support area should be confirmed at least once a year. The integrity check is recommended to be twice or more in the case that conditions of use in the critical area are severe or special considerations are required for the prevention of microbial product contamination.
2. HEPA filters installed in the critical area (Grade A) should be tested for uniformity of air velocity across the filter at installation and thereafter at suitable time intervals. The frequency of integrity check should be determined as stipulated in the preceding Item 1).
3. Pressure difference between the HEPA filter's initial and final pressure loss should be tested at installation and thereafter at suitable time intervals. If filter clogging is severe, it is recommended to include pressure difference monitoring in routine control procedures.
4. When airflow patterns in the APA are altered or suspected of being altered, the patterns should be evaluated to assess the acceptability of the altered patterns.
5. HEPA filters should be tested by leak test as directed in relevant SOPs when any events or circumstances that may damage filter integrity occur or when air quality is judged to have deteriorated.

8. Cleaning and Disinfection of Processing Areas for Sterile Pharmaceutical Product Manufacturing

Processing areas for manufacturing sterile pharmaceutical products should be cleaned and disinfected in accordance with relevant SOPs, and results of cleaning and disinfection should be recorded in writing and retained in an archive.

8.1 Cleaning Agents and Disinfectants

1. Cleaning agents and disinfectants should be validated for their appropriateness and reliability in removing contaminants prior to use. Cleaning and disinfection efficacy should be assessed and confirmed based on type and count of microorganisms characterized by periodic environmental monitoring.
2. Cleaning agents and disinfectants used in the APA should be pretreated with filtration or other appropriate sterilization procedures before use and controlled for the prevention of microbacterial contamination until use, unless commercial products certified to be sterile are used by breaking the envelope immediately before use.
3. When prepared in-house, the preparation of cleaning agents and disinfectants should be pursuant to applicable SOPs, and preparation records should be created in writing and retained in an archive. When commercial products are used after dilution, details of the dilution procedure—such as diluents, dilution ratio, expiration date, storage conditions, and, if applicable, sterilization methods—should be recorded in writing and approved by the quality department.
4. SOPs for the preparation and use of cleaning agents and disinfectants should address the following matters approved by the quality department: types or brands of cleaning agents and disinfectants, cleaning and disinfection schedules, directions for the use of disinfectants, necessity of cleaning following disinfection procedure where necessary, safety precautions for factory personnel, and procedures for management and storage of cleaning tools.
5. When cleaned or disinfected, the surfaces of facilities and equipment that may come into direct contact with pharmaceutical products should be verified by appropriate methods to be free of cleaning agents or disinfectants after the completion of cleaning or disinfection procedures.
6. Reasonable expiration dates should be established for individual disinfectants, and disinfectants should be used before that date.
7. The disinfection of the manufacturing environment should not proceed prior to cleaning, as a rule. If there are any locations in the environment where cleaning agents may reside after cleaning, the cleaning agents should be verified not to impair the efficiency of disinfectants.
8. Disinfectant containers should not be refilled with disinfectants.
9. The selection and use of disinfectants should take the following matters into account:
   (1) The storage and usage of disinfectants should be in accordance with the supplier’s instructions.

(2) The selection of disinfectants should be primarily based on the safety of personnel who are engaged in disinfection processing.

(3) If selected disinfectants might have inferior efficacy against microorganisms isolated from the environment, the efficacy should be reevaluated and the replacement with or alternate use of different disinfectants should be considered and implemented, as appropriate.

(4) If environmental monitoring data indicate or suggest the presence of spore-forming bacteria or fungi, suitable sporicides or fungicides should be selected for disinfection.

(5) The directions for use of disinfectants should include the method of disinfection, application site of the agents, and time required for the agents to exert anticipated effects.

(6) Chemical properties (e.g. corrosivity) which might damage the surface of facilities and equipment to be treated should be assessed prior to the selection of cleaning agents and disinfectants.

10. If use of sporicides or fungicides in processing areas for sterile pharmaceutical products is likely or probable, the type, concentrations, and usage of the agents should be predetermined and specified in writing.

11. The preceding Item 10 should also be applied to the selection and use of fumigating agents (including aerosol formulation), although such application is dependent on the properties of the agents to be used.

12. Cleaning agents, disinfectants, and utensils for applying these agents should not be stored in critical areas. Materials needed for operations in the critical area such as hand sprays to disinfect gloves may be stored in critical areas, if well controlled. If cleaning agents and disinfectants are stored in critical areas, reasons and control procedures for keeping should be defined in writing.

8.2 Validation of Disinfection Procedures

1. The reliability and frequency of disinfection procedures should be established through an environmental monitoring program.

2. Disinfectants should be microbiologically assessed prior to use in each facility, and appropriate control procedures should also be instituted for each facility.

3. The efficacy of disinfectants should be assessed with respect to ensuring that microorganism counts remain below the count predetermined based on the type and count of isolates collected from various surfaces through the environmental monitoring program.

8.3 Monitoring of Adequacy and Efficacy of Cleaning and Disinfection Procedures

1. The adequacy and efficacy of cleaning and disinfection processes should be established through the overall environmental monitoring program.
2. The microorganism counts on the surface of equipment and instruments should be periodically obtained by environmental monitoring and analyzed to detect trends in occurrence and proliferation. A full investigation is mandatory to determine causes of abnormalities when the microbial count exceeds the action level, when the species ratio of microorganisms is obviously different from that routinely reported, or when abnormalities in the count or species ratio continue for an extended period of time. In addition, corrective and preventative measures should be implemented, as appropriate whenever considered necessary.
3. If the established disinfection procedure is not found to be effective for certain types or concentrations of disinfectants, the reliability of such disinfectants should be reevaluated by, for example, comparing the species and counts of microorganisms obtained before and after disinfection.

9. Control of Raw Materials, Containers, and Closures

9.1 Control of Raw Materials (API and Additives)

9. 1.1 General Requirements

1. Procedures for receiving, identifying, storing, sampling, and testing raw materials should be defined as the respective SOPs for control purposes. Acceptance criteria for testing should also be established.
2. Raw materials should be carefully controlled to avoid contamination from receipt until use including storage.
3. Raw materials transferred into the critical area should be confirmed to fall in one of the following categories:
   (1) Certified to be sterile
   (2) Adequately sterilized in accordance with their physicochemical properties and bioburden levels. Their bioburden should be monitored and confirmed to comply with thier specifications at predetermined intervals.
4. Raw materials should be controlled to meet endotoxin specifications.
   (1) If raw materials are not depyrogenated during manufacturing, the endotoxin level of the materials should be ensured to be below the predetermined level.
   (2) If raw materials are depyrogenated during manufacturing, suitable depyrogenation

procedures should be instituted by taking into account physicochemical properties and endotoxin level. Endotoxin content of the materials prior to depyrogenation is preferred to be controlled whenever possible.

9.1.2 Validation

1. When raw materials are required to be sterile, validation should be performed to ensure their sterility.
2. When raw materials need to be sterilized, applicable sterilization procedures should be validated.
3. When individual raw materials are separately sterilized, not only sterilization processes for individual materials but also those for final drug solution should be validated to ensure their sterility.
4. When raw materials are released after sterilization using parametric or dosimetric methods such as steam sterilization and irradiation, such methods should be validated.
5. When raw materials are depyrogenated, the depyrogenation procedure should be validated. Generally, the depyrogenation process must achieve at least a 3-log reduction of endotoxins below challenge.

9.2 Control of Containers and Closures

9.2.1 General Requirements

1. Procedures for receiving, identifying, storing, sampling, and testing containers and closures should be defined as SOPs for control purposes. Acceptance criteria should also be established.
2. Containers and closures should be carefully controlled to avoid contamination from receipt until storage and use.
3. Containers and closures should be washed and cleaned by appropriate and validated procedures. If water is used for washing, water for injection or water of comparable quality should be used for final rinsing.
4. Containers and closures transferred into the critical area should be sterilized by appropriate and validated procedures.
5. Containers and closures should be controlled to meet endotoxin specifications.
   (1) If containers and closures are not depyrogenated after transfer into the critical area, their endotoxin levels should be confirmed prior to transfer to be lower than respective predetermined levels.

(2) If containers and closures are depyrogenated after transfer into the critical area, suitable depyrogenation procedures should be instituted by taking into account physicochemical properties of containers and closures.

6. Sterilized containers and closures should be protected from microbial or pyrogenic contamination by appropriate preventive measures.

9.2.2 Validation

1. Procedures for sterilizing containers and closures should be validated.
2. When containers and closures are depyrogenated, the depyrogenation procedure should be validated. Generally, the depyrogenation process must achieve at least a 3-log reduction of endotoxins below challenge.

10. Storage and Transport of Sterile Intermediate Products

Sterile intermediate products referred to in this section are intermediate products in solution or powder that are stored or transported in a sterile state following aseptic production. This section describes requirements for containers and procedures necessary for maintaining the sterility of intermediate products.

10.1 General Requirements

1. Containers used for the storage and transportation of sterile intermediate products (“containers” in this section refers to cargo transporters, drums, bags, and tanks) should be capable of isolating the products from the surrounding non-sterile environment and hence maintaining the sterility of the products. The containers should be durable enough to withstand handling and environmental conditions encountered during storage and transportation.
2. Containers used for storage and transportation of intermediate products should be cleaned and sterilized before being filled with and storing or transporting the products. Cleaning and sterilization are not required for sterile single-use containers. However, the content sterility must be maintained under all circumstances.
3. SOPs should be established for pouring intermediate products into and discharging them from the containers in a closed system, as a rule. If adopting a closed system is difficult, intervention by personnel should be kept to a minimum.
4. The environment to which sterile intermediate products are exposed should be a critical area (Grade A) free of contamination risks.
5. Sealing performance (tightness) of containers should be checked and confirmed, as required.

10.2 Containers for Storage and Transportation

10.2.1 Design of Containers

The choice of containers for maintaining sterility during storage and transportation of intermediate products should take the following matters into account:

1. The following points should be observed when designing or selecting containers to be used for isolating contents from the non-sterile environment.
   (1) The structure should ensure hermetic sealing.
   (2) If the container cannot be hermetically sealed, the inside of the container should be maintained constantly under positive pressure with sterile gas.
   (3) If sealing performance of container cannot be ensured because of changes in external pressure, air vent filters capable of sterile filtration should be installed and their integrity tested at appropriate intervals.
   (4) Containers should be designed to have a dual structure, as appropriate.
2. If the surface of a container needs to be cleaned and sterilized prior to transferring the container into the APA, the surface should be able to withstand cleaning and disinfection agents.
3. Casters and other parts of transport devices should be protected from generating dust and particulate matter, if such devices are used in the transportation of containers into the APA.
4. If single-use plastic bags are used for storage and transportation, the potential extractable/leachable of components out of the bags into drug solution and effects of the components on product quality should be carefully evaluated and discussed.

10.2.2 Confirmation of Hermeticity

1. Whether or not newly designed containers they can be hermetically sealed should be confirmed.
   (1) Eligibility confirmation at designing

   Sealing performance of container should be estimated by taking into account projected use conditions, including worst-case scenarios.
   (2) Eligibility confirmation at manufacturing (actual use)

   Sealing performance should be tested after storage or transportation under actual use conditions.
2. Sealing performance can be determined by the following example methods:

(1) Check whether or not leakage occurs in containers on hold status under positive pressure.

(2) Check whether or not leakage occurs in containers on hold status under negative pressure.

(3) Immerse containers in pigment solution or bacterial suspension and check whether or not pigment or bacteria are detected in containers.

(4) Inspect containers with a gas leakage detector.

(5) Inspect containers with an electric pin hole testing machine.

10.3 Charging and Discharging Sterile Intermediate Products in and out of Containers

When charging and discharging sterile intermediate products in and out of containers before and after storage or transportation, the following matters should be taken into account:

1. Automatization

   Wherever feasible, automatic charging (including divided charging) and discharging systems should be instituted to minimize personnel intervention.

2. Minimization of personnel intervention-related risks

   If automatic systems cannot be introduced, the following matters should be considered to manage intervention-related risks:

   (1) Working personnel should not physically block or disrupt airflow directed to the charging and discharging ports.

   (2) Charging and discharging operations should be performed in Grade A areas (e.g. clean booth).

   (3) Certain risk reduction measures such as sterile connections using tubing systems that do not require opening of containers should be examined and evaluated.

3. Process simulation

   A process simulation test should be performed to demonstrate the validity of procedures for charging and discharging sterile intermediate products in and out of containers.

4. Limitation of working hours

   Time is always a critical factor for maintaining sterile conditions; the more time required for charging and discharging operations, the greater the risk of contamination. A maximum time limit should preferably be set for these operations, and if more than one container is used per shift, the containers should be marked with identification numbers or other identifiers to facilitate a first-in, first-out order of operations.

10.4 Storage and Transportation Conditions

Potential risks (e.g. temperature, environmental pressure, vibration) that may affect sterility of intermediate products during storage or transportation should be identified, and acceptable working conditions or specifications for such risk factors should be specified. Storage and transportation operations should be conducted with care not to violate established conditions or specifications.

11. Environmental Monitoring

The primary objective of environmental monitoring is to keep manufacturing environments for sterile pharmaceutical products clean by controlling the levels of microorganisms and airborne particles within specified limits for individual APAs and indirect support areas, by monitoring environmental conditions to prevent environmental deterioration and product contamination, and by continuously assessing the efficiency of cleaning, disinfection, and decontamination procedures. Environmental monitoring may be classified into two categories: microbiological and particle control. Microbiological control is not intended to identify and characterize all microorganisms present in the environment but to scientifically estimate bioburden value of the environment, ensure that the manufacture of sterile pharmaceutical products is conducted in an appropriately controlled environment, and implement measures (e.g. disinfection) necessary for maintaining the environment at the required cleanliness level.

11.1 General Requirements

1. Scope of application

   Environmental monitoring should be conducted in critical areas (Grade A) which are APAs, direct support areas (Grade B), and indirect support areas (Grade C or D) adjacent to APAs.

2. Environmental monitoring programs

   An environmental monitoring program and SOPs for implementing the program should be established, and outcome of the implementation should be adequately recorded. The program should be developed by assessing and examining properties of substances to be monitored, frequency of monitoring, sampling locations, and action levels in order to appropriately estimate environmental contamination risks.

3. Monitoring targets

   Monitoring targets are microorganisms and airborne particles.

   (1) Target airborne particles are those ≥ 0.5 μm in diameter. Particles of other diameter (e.g. ≥ 5 μm) should be measured as required by a need of environmental monitoring on an

as-needed basis.

(2) Target microorganisms are bacteria and fungi.

(3) Target microorganisms are airborne bacteria and microorganisms on the surface of walls, floors, fixtures, equipment, gowns, etc.

4. Preparation of environmental monitoring program

An environmental monitoring program should be drawn up prior to performance qualification (PQ) and finalized after PQ completion. Finalization of the monitoring program may require reevaluation of the monitoring program initially developed based on PQ and subsequent inclusion of the monitoring program in the routine control program for routine practice. Since PQ requires performance testing of the worst-case scenario, the numbers of sites and measurement of monitoring targets tend to be large. Reduction in number of sampling locations and frequency is acceptable when the monitoring program is included in the routine control program, as is reduction in frequency of bacterial monitoring by implementing adequate inspection, maintenance, and supervision of equipment on regular and occasional bases, provided the equipment has isolators, RABS, a blow-fill-seal system, or other devices which prove it robust enough to withstand bacterial contamination. Requirements for routine monitoring and control such as the number of sampling site may be reduced by referring to ISO specifications including ISO DIS 14644-1.

5. Monitoring targets and locations

Environmental monitoring targets should also include air in working areas, manufacturing equipment (and process control equipment, where appropriate), and aseptic environments; air for keeping the aseptic environment clean; and compressed air or gas that comes in contact with the environment and equipment. The monitoring frequency of compressed air and gas necessary for manufacturing equipment or used during manufacturing processes as shown in Table 2 may be separately set, provided the cleanliness level can be maintained by integrity test for filters for sterile liquid filtration or other tests.

6. Sampling frequency for environmental monitoring

Sampling frequency should be determined in accordance with air cleanliness level required for individual working areas under both operating and non-operating conditions. The sampling procedures should include specifications on the frequency of sample collection from gown and other stuff. Frequencies of sampling shown in Table 2 may be helpful for establishing the specifications.

7. Monitoring methods: sampling and testing procedures

Optimal number and locations of monitoring points should be determined for individual manufacturing areas by taking into account the size of working area, scope of operations, and

process flows of materials or products. The points should be added as they are considered to be necessary for assessing potential product contamination.

(1) Devices for collecting and counting airborne particles and bacteria should be used after validated calibration. Results of particle counting should be converted to the count per-cubic-meter of atmosphere (/m^3).

(2) Sampling for collecting airborne microorganisms should be conducted via one or more suitable procedures including settle plate, impact, and filtration methods, and collecting microorganisms on the surface should be conducted via one or more suitable methods such as contact plate or swabbing. The size of the area to be sampled should be determined in accordance with the shape and surface condition of equipment and apparatuses. In principle, the recommended sampling area of equipment and apparatuses is 24 to 30 cm^2. Air volume to be sampled for airborne microorganism monitoring should be decided by overall considerations and discussion of factors involved, such as cleanliness of the target area and routine monitoring frequency. If the target area is Grade A, microbial count monitoring usually uses a circular flat plate of 90 cm in diameter, and the maximum exposure time is 4 hours.

(3) The culture medium used for the detection and enumeration of airborne and surface microorganisms should be suitable for the growth of target microorganisms such as aerobic bacteria, fungi (i.e. yeasts, molds), and anaerobic bacteria. The medium should be tested for the absence of cell growth inhibitory substances to select a competent medium suitable for microbacterial monitoring. The objective of testing for cell growth inhibitory substances is to confirm that the collection and growth of microorganisms will not be affected by the presence of alcohol, antibiotics, etc. and to ensure that monitoring results are not altered by the quality of medium used.

(4) The incubation temperature of the medium should be suitable for the growth of target microorganisms.

8. Alert and action level specifications

Alert and action levels should be established for individual target substances and locations to be monitored.

(1) Action level specifications may be established by referring to data contained in Table 3. Caution should be exercised not to underestimate the contamination risk by averaging particle or microbacterial count. If microorganisms are detected in a Grade A area, the effect of such microorganisms on product quality should be evaluated even if the count meets acceptable criteria.

(2) Alert level specifications should be established based on results of PQ tests.

(3) The monitoring program should include actions and measures to be taken (i.e., investigation of causes of non-compliance, suspension of manufacturing) when alert or action level specifications are met. In principle, a deviation from the alert level specifications does not require a suspension of manufacturing but other appropriate actions or measures should be taken. Deviations from the action level specifications should be investigated for cause(s) prior to shipment of final products manufactured through the process where the deviation occurred, and corrective measures should be taken. The validity of corrective measures taken should be verified to confirm the recovery of acceptable environmental conditions, as needed. The recovery may be readily confirmed in some instances by, for example, counting particulate matter, but not reproducible in other instances, such as with bacteria adherence to gowns. If the cause(s) cannot be traced, recovery should be established by general approaches including prohibition of personnel entry for a certain period, retraining of personnel, and reviewing assigned tasks.

11.2 Routine Monitoring and Control

1. Implementation of the monitoring program

   Monitoring of microorganisms and particulate matter should be routinely performed in accordance with the monitoring program.

2. Microbiological control

   The microbiological environmental monitoring program should be routinely performed to monitor potential microbial contamination. The program should include periodic investigation on characterization of environmental flora and isolates to assess contamination risks to pharmaceutical products.

3. Sampling

   Sampling of surfaces that come in contact with pharmaceutical products or other materials in critical areas should be performed immediately after the completion of filling or other aseptic processing operations.

4. Gases for manufacturing processes

   Gases that may directly contact pharmaceutical products, primary containers, and surfaces that come into direct contact with pharmaceutical products should be periodically inspected and controlled to ensure the absence of microorganisms.

5. Routine analysis

   For the adequate maintenance of the manufacturing environment, data obtained from routine

monitoring should be analyzed to detect any trends in changes in the environment and establish monitoring limits for trend analysis. Even if changes in the environment do not deviate from the specified limits (the alert level), any trends suggesting variations from normal conditions (trend analysis level) should be predicted and the cause(s) investigated to maintain the quality of the environment at an appropriate level. Trend analysis results should also be utilized for the maintenance of equipment for environmental control, such as the HVAC system, and for optimization of sterilization and disinfection procedures.

11.3 Example Assessment Criteria for Environmental Monitoring

Table 2 shows example frequencies of environmental monitoring classified by the cleanliness level, and Table 3 shows acceptance criteria for airborne particulate matter and microorganism counts. Since the risk of contamination varies depending on the formulation and size or volume of pharmaceutical products, structure/function of manufacturing equipment, automation level, time of retention of closures, and availability and performance of equipment for environmental control such as the HVAC system, the environmental monitoring program should be prepared and implemented by taking these factors into account:

1. The frequency of microbiological monitoring may be increased or decreased depending on the type and time of processing activities; however, the frequency needs to be adequate for effective monitoring of potential microbiological contamination of pharmaceutical products.
2. The frequency of microbiological sampling from the surface of personnel gown and other stuff should be commensurate with ability and experience of individual personnel. For example, sampling frequency should preferably be increased for operators with less aseptic processing experience. The ability and experience of personnel should be collectively evaluated based on the frequency of engagement in aseptic processing, microbacterial monitoring data, frequency of participation in media fill tests, etc.

3) The monitoring frequency for Grade C and D areas should be determined by the types of pharmaceutical products, processes, operations, etc. to be performed in the areas for appropriate quality control and risk management. The frequency may be decreased if the risk of contamination is low, such as when pharmaceutical products are not exposed to the environment.

4. Monitoring should be reinforced immediately after facility operation is started (beginning of PQ), restarted after long-term shutdown, or partially changed.
5. When personnel enter a Grade A area from a Grade B area, surface microbacterial count on gowns and other stuff should be evaluated against stricter acceptance criteria (those for Grade A area) depending on the level of product contamination risk.

6. Sampling of particulate matter in Grade A and B areas should preferably be conducted via continuous monitoring from equipment assembly until completion of critical operations.
7. The monitoring of particulate matter during times when no manufacturing operations are taking place should be conducted on an as-needed basis to maintain the environment at predetermined cleanliness levels and thereby, for example, detect malfunctions in the air conditioning system.
8. Assessment results of particulate matter monitoring may differ depending on the amount of air sampled and air suction capacity of monitoring devices. Air samplers and assessment method should be appropriate for the particulate matter control system used.

Table 2. Frequency of Environmental Monitoring for Microbacterial Control

Cleanliness grade		Airborne particulate matter	Airborne microorganisms	Surface microorganisms	
				Equipment and walls	Gloves and gowns
A		During processing	Every working shift	After completion of processing	After completion of processing
B		During processing	Every working shift	After completion of processing	After completion of processing
C, D	Area in which products and containers are exposed to the environment	Once a month	Twice a week	Twice a week	----
	Other areas	Once a month	Once a week	Once a week	----

Table 3. Acceptance Criteria for Environmental Microorganism Count (during Operations)

note 1

Cleanliness grade	Airborne microorganisms		Surface microorganisms	
	Air (CFU/m^3)	Settle plate Note 2 (CFU/plate)	Contact plate ($CFU/24–30\ cm^2$)	Gloves (CFU/5 fingers)
A	< 1	< 1	< 1	< 1
B	10	5	5	5
C	100	50	25	–
D	200	100	50	–

Note 1) Acceptance criteria are expressed as mean values.

Note 2) Measurement time per plate is 4 hours at maximum and the measurement is performed during processing operation.

12. Qualification of Equipment and Utilities

12.1 General Requirements

1. In this section, the term “equipment” refers to equipment used for sterilization, filtration, filling, capping, freeze-drying, and sealing in the manufacture of sterile pharmaceutical products in the APA, as well as HVAC system, incubators, fermentors, and cleaning equipment installed, as required, in indirect support areas.
2. In this section, the term “utilities” refers to systems for supplying different qualities of water, pure steam, compressed air, and different kinds of gases in the manufacture of sterile pharmaceutical products.
3. For the qualification of equipment and utilities, qualification protocols and SOPs should be established to define assignment of responsibility of individual personnel and other related matters. Equipment and utilities used for the manufacture of sterile pharmaceutical products should be designed so as to have minimum influence on the sterility of the products. The structure or shape and components materials of equipment and utilities should be selected to make it easy for cleaning, disinfection, sterilization, and maintenance. Special attention should be paid to the surface of equipment and utilities to which pharmaceutical products, component materials, water, steam, or gases etc. may be directly exposed.

4. Flow lines for sterile pharmaceutical products, sterile raw materials, and other sterile materials should beadequately designed by taking into account personnel movement and airflow patterns.
5. Personnel movement and intervention into sterile pharmaceutical products should be designed to be minimum. In addition, operation, maintenance, repair, and adjustment of equipment should preferably be performed from outside the critical area, whenever feasible.
6. Generation of turbulence and particles in critical areas should be controlled to a minimum. The flow of clean air from supply vent to return or exhaust vent should be optimally designed in direct and indirect support areas.
7. Equipment should be laid out so as to minimize the physical burden on operators.
8. Requirement specifications (user requirements specifications, URS) for equipment and utilities should be defined in writing with regard to required quality levels, facility capacity for amounts of use during manufacture, applicable regulatory requirements (e.g. laws, regulations, guidelines), quality of component materials, and performance, etc., and DQ should be conducted in accordance with the URS.
9. The duration of exposure of sterile pharmaceutical products, surface of equipment that may contact with sterile pharmaceutical products, and containers uncapped, should be kept as short as possible. 10. IQ should verify that the equipment and utilities have been installed as directed in relevant design specification in accordance with written procedures.
11. OQ should verify that equipment and utilities have a capacity of performance as required by their specifications. If the equipment and utilities are to be operated or used in APAs, it should be verified that the required cleanliness in the APAs is maintained throughout operation or use.
12. All processes conducted in the APA that may influence the sterility of pharmaceutical products should be scientifically evaluated and appropriately validated.
13. Operational procedures for all key equipment and control parameters, and theire acceptable limits should be described in relevant SOPs in an appropriate manner.
14. Validation of the processes utilizing cleaning, sterilizing, incubating/fermenting, filtering, filling, capping, freeze-drying, and sealing equipment should be conducted to assess the sterility assurance level of pharmaceutical products in each of these processes. Sterility assurance levels may be validated together for multiple processes using different equipment if the processes are continuous.
15. The sterility of equipment surfaces that may come into direct contact with sterile pharmaceutical products should be validated.
16. OQ studies should be conducted for utilities including CIP/SIP systems and equipment that

supply purified water, water for injection, compressed air/other gases, pure steam, etc.

17. Validated period for use of the equipment after sterilization should be established to ensure the sterility of sterile pharmaceutical products. If critical process changes are made, the potential impact of the changes on validated period foruse should be reevaluated.

18. Since design concepts applicable to aseptic manufacturing of sterile pharmaceutical products vary, any additional techniques available for promoting sterility assurance should be positively employed whenever available.

19. When sterilization equipment is a continuous system, conveyor belts should not pass through a partition between an APA and a processing area of lower air cleanliness, unless the belts themselves are continuously sterilized (e.g. heat sterilization tunnel). When a continuous sterilizer is used, airflow should be monitored to ensure that air does not flow from a non-sterile to sterile area during processing.

12.2 Equipment Maintenance

1. For the preventative maintenance of equipment and utilities, maintenance protocol and SOPs should be prepared to define the assignment of responsibility of individual personnel and other related matters.

2. SOPs should also be prepared for cleaning, disinfection, and sterilization procedures for equipment and utilities and their use permission in subsequent manufacture. The procedures for cleaning, disinfection, and sterilization should be as specific and detailed as possible to achieve cleaning, disinfection, and sterilization of equipment in an efficient and reproducible manner. These procedures should address the following:

   (1) Assignment of responsibility of individual personnel for cleaning, disinfection, and sterilization of equipment and utilities

   (2) Cleaning, disinfection, and sterilization schedules

   (3) A complete description of the procedures, instruments, apparatuses, and agents used for cleaning, disinfection, and sterilization (including a procedure for diluting cleaning agents) of equipment and utilities

   (4) Instructions for disassembly and reassembly of pieces of equipment and utilities necessary to ensure adequate cleaning, disinfection, and sterilization, where appropriate

   (5) Instructions for the removal or deletion of description regarding previous batch

   (6) Instructions for preventing contamination of cleaned equipment and utilities until next use

   (7) Inspection of equipment and utilities to confirm cleanliness level and sterility

immediately before use, if feasible

(8) Maximum allowable time for cleaning, disinfection, and sterilization of equipment and utilities after completion of manufacturing, where appropriate

3. Equipment and utilities should be kept after cleaning, washing, drying, preserved, and, when necessary, disinfected or sterilized to minimize their influence on the sterility of sterile pharmaceutical products.
4. When successive lots of the same sterile pharmaceutical product are produced, one at a time and in succession, using the same equipment and utilities for continuous or period (campaign) production, the equipment and utilities should be cleaned, disinfected, and sterilized at intervals that have been validated as effective for the prevention of microbial contamination.
5. The evaluation of cleaning, disinfection, and sterilization of equipment and utilities used in the manufacture of sterile pharmaceutical products like vaccines containing live microorganisms per se or other ingredients of bacterial origin should include the evaluation of efficiency of these procedures in removing microorganisms and other ingredients of bacterial origin. The evaluation of sterilization efficiency may be omitted when target microorganisms have been documented to be less resistant to these processes than microorganisms specified in the Japanese Pharmacopoeia or other official compendia.
6. The procedures for cleaning and for selecting cleaning and disinfecting agents should be specified and justified with rationale and adequate evidence.
7. All equipment and utilities should be identified by appropriate methods based on materials or products to be processed and cleanliness levels required.
8. If stopped for repair or inspection, equipment and utilities should be disinfected or sterilized prior to resumption of operation, as required.

12.3 Calibration

1. For the calibration necessary for the control, measurement, and monitoring of equipment and utilities critical in ensuring the sterility of pharmaceutical products, calibration protocol and SOPs should be established to define assignment of responsibility of individual personnel and other related matters. These SOPs should then be followed for calibration.
2. The calibration of equipment and utilities should be performed using certified and traceable standards, whenever available.
3. Records of the above-mentioned calibration procedures should be maintained.
4. The current calibration status of critical equipment and utilities should be known to relevant personnel and verifiable.

5. Instruments that fail to meet calibration criteria should not be used.
6. When a critical instrument for ensuring the sterility of sterile pharmaceutical products shows deviations from approved standard calibration values, investigation and assessment of the deviations should be conducted to judge whether or not the deviations have affected sterility of pharmaceutical product lots manufactured in an environment which has been controlled, measured, or monitored by the instrument of concern since its last calibration.

12.4 Change Control

1. For the confirmation, verification, approval, and recording of changes in equipment, utilities (including parameters), and procedures which may be critical in ensuring the sterility of pharmaceutical products, change control SOPs should be established to define assignment of responsibility of individual personnel and other related matters.
2. Changes referenced in Item 1 above should be drafted by an assigned person, reviewed by a qualified person, and approved by the quality department, since such changes carry a risk of altering the capacity and performance of equipment affecting the quality of pharmaceutical products.
3. Proposed changes should be evaluated concerning their potential impact on sterility of pharmaceutical products from the viewpoint of risk management. The impact evaluation should be based on points of consideration referred to in Article 12.1 above.
4. Prior to the implementation of approved changes, all SOPs should have a provision ensuring revision of all documents to be affected by approved changes.
5. Personnel responsible for operating equipment affected by approved changes should be trained prior to the implementation of the changes.
6. The potential impact of approved changes on the valid time of use of sterilized equipment should be assessed to ensure the sterility of sterile pharmaceutical products.

13. Sterilization Process

13.1 General Requirements

1. Containers and closures that come into direct contact with pharmaceutical products and the surfaces of equipment that may come into direct contact with intermediate products after sterilization should be sterilized by methods appropriate for maintaining the predetermined sterility assurance level.
2. Equipment surfaces that may come into direct contact with containers and closures should also be sterilized as required for maintaining the predetermined sterility assurance level.

3. Materials to be sterilized should be handled by techniques appropriate for avoiding mix-ups of sterilized and unsterilized materials.
4. Already-sterilized materials should be treated with appropriate preventive measures to avoid re-contamination. As a rule, such materials should be handled in accordance with the aseptic processing procedures recommended in this guidance, particularly when directly exposed to the environment.
5. Sterilization processes for sterilizing pharmaceutical products and materials in critical areas should be individually validated and also periodically evaluated at least once a year.
6. History of sterilization equipment usage should be adequately controlled and maintained by, for example, keeping logbooks.
7. Sterilization-related procedures and control parameters for process control, routine monitoring and control, maintenance and control, supplies, and sterility verification should be fully documented.

13.2 Autoclaving

1. The quality of steam used for sterilization should be ensured not to adversely affect the function and safety of materials or equipment to be sterilized. The generally recommended procedure is to use vapor (pure steam) generated from purified water or water of high quality. Condensate water resulting from the vapor should also meet specifications for water of higher purity than that used for product formulation. The description of vapor should be periodically inspected, and causes of quality deterioration should be investigated, whenever suspected, in order to implement proper corrective measures.
2. Appropriate control procedures (e.g. visual inspection procedure, maximum allowable frequency of steam cleaning) should be established for the sterilization of materials to be used repeatedly (e.g. filters, utensils, aseptic gowns) to ensure maintenance of specifications, safety, and intended functions after repeated exposure to steam at its maximum intensity. Accordingly materials for repeated use should be properly managed by the control procedures.

13.2.1 Sterilization Process

1. Acceptable limits of sterilization-related process parameters should be established and documented.
2. When the sterilization process includes air purging, methods and specifications should be established for measuring and evaluating the maximum acceptable limits of air leak volume for sterilization equipment and permissible residual volume of non-condensable gas in

materials to be sterilized.

3. If air or water come into direct contact with materials to be sterilized during the sterilization process, their purity and physical characteristics (e.g. pressure, temperature) should not adversely impact the intended performance or safety of the materials.
4. Commercial biological indicators (BIs) and chemical indicators (CIs) used in the verification of the sterilization process should conform to international standards or other official specifications.
5. When the validity of a certain sterilization process is tested by simulation using a dummy load, the validity, efficacy, and time limit of use of the load should be verified and documented.
6. When the sterilization process includes a procedure or procedures other than sterilization (e.g. drying), the assessment method for such a procedure or procedures should be established, documented, and implemented for appropriate control.
7. Pretreatment procedures in the sterilization process (e.g. cleaning) should be defined with appropriate conditions and controlled accordingly so as not to impair the validity of the sterilization process.

13.2.2 Sterilization Equipment

1. Key properties of sterilization equipment including manufacturer's name, type, size, structure, materials of construction, functions, and capacity, should be available in writing. The user manual should also be available with the following outlined: methods of standard operation, default setting, emergency responses, disassembly and reassembly, maintenance control (including calibration), etc.
2. Sterilization equipment should have basic performance requirements for sterilization such as establishment of operational parameters and processing capacity.
3. Parts of sterilization equipment that are exposed to the stress of sterilization procedures (e.g. inner wall surface, pipes) should be made of materials resistant to such stress. The materials should not release any substances that may have undesirable effects (e.g. interactions, decomposition, absorption) on the quality of sterilization processes or pharmaceutical products.
4. Utilities such as electricity and compressed air should be constantly supplied to sterilization equipment to ensure consistent operation throughout the sterilization process.
5. When materials to be sterilized are not hermetically sealed, gas used for aeration or pressure recovery should be sterilized. Filters used for gas sterilization should have a structure suitable for sterilization and be made of materials resistant to sterilization procedures. In addition,

filters should be tested for their integrity to ensure the sterility of gas to be supplied.

6. Cycle parameters of sterilization equipment necessary for monitoring sterility of materials or products should be freely established in ranges suitable for the control of sterilization processes and easily managed with excellent reproducibility. Sterilization patterns of the equipment should also be easy to establish depending on properties and physical state of materials to be sterilized.
7. Sterilization equipment should be equipped with functions (e.g. computerized system control) that enable the sterilization cycle to proceed accurately. If the equipment is of the continuous cycle type, there should be a function that enables the correct transfer of products into and out of the sterilizer chamber.
8. Sterilization equipment should be equipped with appropriate sensors and recorders for the measurement and control of critical cycle parameters to achieve the required level of sterilization. The specifications (e.g. type, precision, materials), location, and other requirements for the sensor should be selected based on characteristics and required conditions of the sterilization process to be run with the equipment.
9. Sterilization equipment should have a function to ensure maintenance of conditions permissible for anticipated sterilization processing at all times during operation. It is recommended that alarming and recording systems which function in response to the type and severity of emergency be installed. It is also recommended that safety devices (e.g. safety valves) be installed to prevent major accidents.
10. The location where sterilization equipment is installed should have sufficient space for the operator to work and should be maintained at the required cleanliness level.
11. Sterilization equipment should be designed to facilitate easy manual operations by the operator, such as operation of control buttons and transfer of pharmaceutical products into and out of the chamber.
12. If the computer system for manufacturing control or other purposes is connected to and controlled by a higher-level host computer, input/output data, control specifications, and other processing should be precisely documented.
13. SOPs should be established and documented to ensure reflection of physical changes and process changes made to sterilization equipment in the specifications for the equipment.

13.2.3 Validation of Sterilization Procedures

The method for validation of autoclave cycles comprises tests on heat distribution in the sterilization chamber, heat permeability of sterilization load, and verification of sterilization capacity

using BIs. This validation also serves as PQ of sterilization equipment.

1. A heat permeability test should be conducted using materials to be actually sterilized. Except for samples for temperature measurement, it is acceptable to use a reference load instead, provided the use of the reference load can demonstrate scientific validity of its use based on physical data obtained
2. The heat permeability test should be conducted for different patterns of loading including maximum load, at least 3 times for each pattern. The minimum loading pattern test should be conducted as required. Pictures or photographs showing loading patterns used in the test should be recorded.
3. The heat permeability test may be conducted by grouping products and loading patterns if the grouping is acceptable with regard to type and properties of materials to be sterilized and batch sizes for sterilization.
4. Locations of verification thermometers should include cold spots of materials to be sterilized and, as appropriate, hot spots.
5. The temperature at cold spots should be confirmed with a thermometer to verify that predetermined sterilization conditions for materials to be sterilized have been attained with heating.
6. The accomplishment of sterilization at cold spots should be verified using relevant BIs. For details on available BIs, refer to ISO 14161 (Sterilization of Health Care Products—Biological Indicators: Guidance for the Selection, Use and Interpretation of Results).
7. When sterilization cycles are established based on bioburden determination with materials to be sterilized, the count and resistance of BIs and assessment methods for these parameters should be selected based on predicted or established bioburden levels.
8. The integrity of materials to be sterilized should be verified by established sterilization cycles.
9. The time for sterilization cycles should be confirmed to be compatible with the time schedule of actual manufacturing.
10. If heat distribution is determined using a thermometer not originally provided with sterilization equipment, the thermometer should be calibrated before and after the determination.
11. Sterilization equipment should be validated again if the structure of the equipment is modified, if loading conditions for materials to be sterilized are changed, or if utilities supply conditions are changed. The scope and frequency of revalidation are dependent on risk of inadequate sterility assurance of pharmaceutical products.
12. The sterilization of porous materials should be conducted after carefully establishing

sterilization cycles to achieve thorough sufficient ventilation to replace air deep in the materials with vapor.

13. Air inside the chamber of the sterilizer should be periodically confirm to be completely removed during sterilization cycles. This check should be added to routine monitoring and control items, as required. The typical air removal test is the Bowie-Dick test.

13.2.4 Routine Monitoring and Control

1. Process parameters and control items necessary for routine monitoring and control of the sterilization process should be determined and documented based on validation data. The validity of the process parameters and control items should be verified by confirming reproduction of specified conditions of sterility for individual materials to be sterilized.
2. Test items as well as detailed operating procedures and frequency of testing should be documented for periodic check-ups, maintenance control, calibration, and equipment.
3. Routine management and control of the sterilization process should be performed on a cycle-by-cycle basis.
4. Data on sterilization cycle-related parameters should be obtained and recorded to verify that sterilization of materials has been successfully achieved. Recorded data should include readings of the inner pressure and temperature of the sterilization chamber in each sterilization cycle.
5. The completion of sterilization cycles within specified limits of relevant specifications should be verified by direct measurement of selected cycle parameters, and obtained results should be recorded. If necessary, BIs and CIs should also be monitored.
6. A leak test should be periodically performed when the sterilization process incorporates an air elimination process for steam penetration. Any additional checks on performance other than sterilization (e.g. drying of materials to be sterilized) that may have potential influence on product quality should be conducted and recorded according to written procedures.

13.2.5 Handling of Sterilized Materials

1. SOPs should be prepared and implemented for handling materials following completion of the sterilization process. The SOPs should include methods and criteria for assessing sterilized materials to confirm that the sterilization process has been adequately conducted to comply with relevant requirements. When additional parameters (e.g. BIs, CIs) other than process parameters are required for the assessment of complete sterilization, specifications to be met with such parameters should be included in the assessment criteria.

2. The SOPs should also specify procedures for obtaining and storing various records of sterilization processing. The records should include information on the following matters and be reviewed and approved by the supervisor:
   (1) Time started and ended and date of sterilization processing
   (2) Sterilization equipment used
   (3) Materials sterilized
   (4) Sterilization conditions employed
   (5) Assessment criteria and results of sterilization processing
   (6) Records of physical process parameters (e.g. temperature, pressure, etc.)
   (7) Identification of sterilized materials and their traceability
   (8) Operators' names

   When sterilization is carried out by a batch process, retrospective investigations of the sterility of sterilized materials can be easily traced by allotting batch numbers to individual processing.
3. If any materials are judged not to have been adequately sterilized, such materials should be handled in accordance with relevant SOPs. Causes of inadequate sterilization should be investigated and appropriate corrective actions implemented.
4. Sterilized materials should be stored under conditions suitable for preserving and maintaining their sterility and other properties. The location, method, environmental conditions, and duration of storage should be predetermined and managed accordingly.

13.3 Dry Heat Sterilization

Basic requirements and control methods for dry heat sterilization should be consistent with those specified for autoclaving. Additionally, the following dry heat sterilization-specific control measures should be met.

1. The dry heat sterilization process should be validated via endotoxin challenge test or other appropriate method when the process requires depyrogenation.
2. Materials to be sterilized should be periodically tested for pre-sterilization endotoxin content.
3. HEPA filters mounted on sterilization equipment should be periodically tested for leaks to check the capacity of the filters. The test should ideally be performed once every 6 months or at least once a year.

13.4 Electron Beam and Gamma Ray Sterilization

Basic requirements and control procedures for electron beam and gamma ray sterilization should be consistent with those specified above for autoclaving. Additionally, the following criteria specific to electron beam and gamma ray sterilization should be met:

1. The dose of radiation necessary for achieving complete sterilization should be determined based on acceptable validation data.
2. Sterilization process parameters should be established based on appropriate validation data. Adequate records verifying that the irradiation has been performed in accordance with the process parameters should be obtained and recorded.
3. Bioburden assay of materials to be sterilized should be performed prior to sterilization at a predetermined frequency.
4. The loading configuration of materials to be irradiated should be evaluated and documented based on validation data. Procedures for adequate storage and control of materials before and after sterilization should also be documented.
5. The name, loading configuration, quantity, irradiation date, and dose absorbed should be controlled for irradiated materials. These materials should be identified in an appropriate manner (e.g. sterilization batch number) to ensure the traceability of individual materials.
6. Irradiated materials should be placed in the smallest packaging units available for storage and control and labeled as “irradiated” in a readily accessible location outside the container.
7. The radiation dosage measurement system should ensure traceability of measurement results to national standards.
8. When the irradiation sterilization process is contracted out, the consigner and consignee should agree to at least the following matters in writing:
   (1) Preservation of the sterility of consigned goods during transportation
   (2) Preparation of consignee’s statement certifying that consigned goods have been sterilized
   (3) Disclosure of sterilization conditions, upon request by the consigner, for each lot of consigned goods, as appropriate
9. The predetermined radiation dosage should be periodically checked at appropriate intervals to ensure the efficacy of irradiation sterilization cycles (sterilization dose audit).

13.5 Other Sterilization Methods

Basic requirements and control procedures for electron beam and gamma ray sterilization should be consistent with those specified for autoclaving. Additional control measures specific to

electron beam and gamma ray sterilization should be established and implemented, as appropriate.

14. Clean-In-Place System

A clean-in-place (CIP) system is a cleaning method which is designed to clean an entire system of equipment with appropriate cleaning agents *in situ* without any disassembly of equipment components, or pipes. Points to consider in designing equipment to be subjected to CI P and in implementing the system are summarized below. Points to consider in implementing the system should also be applied to general cleaning operations.

14.1 Design Considerations for the CIP System

When designing equipment, pipes, cleaning agent supply apparatus, etc. for the CIP system, the following technical points should be considered:

1. Equipment and piping with smooth inner surfaces should be selected and incorporated into the CIP system to facilitate cleaning effectiveness. The CIP system should be designed to allow for prompt confirmation of cleanliness level after completion of the CIP process.
2. Presence of “dead legs” in piping connected to the equipment should be minimized. The equipment, piping, and valves within the equipment should have designed to have adequate slope to allow for draining of both cleaning agents.
3. The cleaning agent supply portion of the CIP system should be designed to maintain constant flow rate, pressure, temperature, and concentration of cleaning agents.
4. When equipment and/or pipes to be subjected to CIP are washed by dividing them into several segment, the segments should overlap o ensure that all portions of the system are adequately and effectively cleaned.
5. After completion of a CIP process, equipment or systems much be able to be stored in a manner which prevent recontamination.

14.2 Selection of Cleaning Agents

1. Cleaning agents should be selected after evaluating their ability to remove residual substances, physicochemical properties of residual substances to be removed, and compatibility with manufacturing equipment. All components of cleaning agents must be removed to levels below specified detection limits before starting the final rinsing process.
2. Examples of cleaning agents include water, hot water, detergents, alkaline solutions, hot alkaline solutions, and organic solvents.
3. The quality of water used for final rinsing of product contact equipment surfaces should be of

the same quality as water used for product formulation.

4. Quality control specifications of cleaning agents should be established and documented.

14.3 CIP Process Parameters

The most difficult to clean locations within a CIP system should be identified at the validation stage, and if necessary additional cleaning operations or processes should be developed and verified for cleaning efficacy. Based on validation results, CIP process parameters to achieve the acceptable level of cleanliness should be specified and documented for the control of the cleaning process to achieve the predetermined level of cleanliness. The CIP process parameters should include the following:

1. Type and concentrations of cleaning agents
2. Flow rate of cleaning agents
3. Duration of contact between the equipment or process surfaces and cleaning agents.
4. Temperature and pressure of cleaning agents
5. Total cleaning time
6. Control parameters that indicate the acceptable residual substances after completion of CIP, such as conductivity, pH, and total organic carbon (TOC) (to be determined based on the composition of cleaning agent)
7. Maximum allowable time until start of CIP process after completion of the manufacturing process (Maximum allowable time should be controlled to avoid so as not to be hard to remove the residual substances by elapsed time until start of CIP.)

14.4 Routine Monitoring and Control

The technical performance of each CIP system should be recorded and data retained for periodically review. CIP and related records should include, but not be limited to, the following:

1. Time and date
2. Name of equipment cleaned
3. Name and production batch number of pharmaceutical products manufactured prior to CIP cycle
4. Name and production batch number of pharmaceutical products manufactured after cleaning with the CIP system
5. Names of CIP operators
6. Operating conditions of the CIP system

7. Verification of the compatibility of CIP conditions employed
8. Allowable time between the completion of the CIP processing and the use of equipment cleaned with the CIP system
9. Validity of calibration of instruments used to detect the completion of cleaning process and indicate CIP process parameters such as flow rate and pressure, etc. .

14.5 Maintenance and Control

Critical equipment such as pumps, which are closely related to CIP parameters including pressure, temperature, and flow rate, should be well controlled and subjected to maintenance at defined intervals. When critical equipment is replaced, new replaced equipment should be selected as equivalent performance. Replaced equipment should be assessed and documented to achieve equivalent cleaning efficiency.

14.6 Personnel Training

The education and on job training programs for personnel engaged in CIP operations should cover at least the following:

1. Design and functions of the CIP equipment and an operational outline of CIP process
2. Possible corrective actions to be taken in the event of deviations or OOS results in the CIP process
3. Any other technical issues of significance in the operation of a specific CIP process.

15. Sterilization-In-Place System

A sterilization-in-place (SIP) system is a sterilization method which is designed to sterilize an entire system of equipment *in situ* without disassembly of components, or piping. The most common sterilizing agent for SIP is saturated steam (moist heat).

15.1 General Requirements

1. When equipment (e.g. tanks, filling lines, transfer lines, filtration system, water for injection systems) that cannot to be sterilized by autoclaving due to size or shape is subjected to sterilization-in-place (SIP), the efficacy of SIP (typical sterility assurance level [SAL]: $\leq 10^{-6}$) should be demonstrated by an appropriate measuring instrument such as temperature gauge, pressure gauge, thermocouple, and moist heat-resistant BIs. Care must be taken to ensure that the placement of these BIs does not obstruct the flow of steam or the ability of the system to

drain condensate.

2. Steam used in the SIP process should be generated from purified water or water of not less than purified water grade. Condensed water from steam should meet specifications of water used for product formulation.
3. Locations most difficult to sterilize so-called “cold spots” in the equipment should be identified, and the SAL achieved at these spots should be evaluated are appropriate intervals.
4. Equipment integrity should be maintained after completion of SIP. Steam and condensate should be purged from the SIP system by either sterile compressed air or nitrogen gas, and the system should be maintained under positive pressure until it is used for processing. For any equipment which may be operated under negative pressure or atmospheric pressure, a qualification test must be performed to confirm that the sterility of the entire equipment is not compromised. The maximum allowable time between the completion of SIP and the use of the equipment should be specified and verified.
5. When the equipment is not equipped with an automatically controlled and valve sequenced SIP system, manual SIP procedures should be established and then strictly complied with, and critical procedures of the system should be double-checked. Records of manual SIP operations, when performed, should be maintained as evidence that the operations were conducted as stipulated in the procedures.

15.2 Key Design Considerations for the SIP System

SIP equipment should be confirmed to be compatible with steam to be used and pharmaceutical products to be sterilized and should be designed not to retain air or condensed water within the equipment. The following matters should be taken into account:

1. Smoothness of inner surfaces of the equipment
2. The design must ensure that saturated steam to reach all surfaces to be sterilized
3. Location of the saturated steam inlet and steam distribution
4. The system design should avoid the formation of air pockets within the SIP system and ensure that condenses water is efficiently drained from the system.

   There should not be unnecessary piping branches and dead legs should be minimized
5. All piping should be properly sloped to allow for adequate draining.
6. Appropriate location for steam and steam condensate discharge
7. Heat and pressure resistance of the equipment
8. Compatibility between construction materials and steam quality

9. Measures necessary to maintain sterility of the systems to be sterilized during and after SIP processing, such as the installation of appropriate vent filters and maintenance of positive pressure

9. When equipment and/or pipes are sterilized by dividing them into several segment, the segments should overlap o ensure that all portions of the system are adequately and effectively sterilized.

15.3 Routine Monitoring and Control

1. When equipment to be subjected to SIP is washed by certain cleaning procedures, including the CIP system, SIP processing should also be performed promptly after the completion of CIP or washing. Data on SIP processing should be recorded and retained for each SIP process and periodically reviewed for completeness and correctness. It is recommended that the following parameters should be monitored and recorded continuously from the introduction of steam until completion of SIP for each SIP operation: temperature (e.g. supply steam, inside tanks, drain ports), pressure (e.g. supply steam, inside tanks, inside of pipes), and duration of SIP operation. If continuous measurement and recording are not feasible, alternate monitoring and recording methods should be instituted to confirm that processing requirements for sterilization parameters have been met.
2. Process operation records and other records on SIP operations should include, but not be limited to, the following:

- Time and date
- Names of equipment subjected to SIP
- Names of operators
- Operation conditions
- Verification of compatibility of SIP conditions employed

3. An appropriate system should be established for distinguishing the status of equipment before and after SIP processing.
4. Filters for sterilizing gas and vent filters for tanks and chambers used in the SIP process should be periodically tested for integrity to ensure that they functioning properly.
5. Critical instruments such as thermometers should be calibrated at appropriate defined intervals.

15.4 Maintenance and Control

Valves and steam traps should be subject to periodic maintenance checks to ensure the proper

injection of steam for sterilization and that condensed water forming during SIP is properly discharged. If the shape and size of pipes to be sterilized by the SIP system or steam supply conditions are modified, such modifications should be subject to change control, documented and validated.

15.5 Personnel Training

Education and training programs for personnel engaged in SIP operations should cover the following:

1. Design and functions of the SIP equipment and an operational outline of SIP process
2. Appropriate countermeasures that may be taken to correct abnormalities in the SIP process
3. Any issues that are deemed by the user to be critical in the performance and assessment of the SIP system

16. Aseptic Filling Processes

16.1 General Requirements

Aseptic filling processes should meet the following requirements:

1. SOPs for aseptic filling processes should be established describing in detail each operation procedure for all the steps starting from the preparatory stage including the filling machine assembly to sterilization, stoppering, capping, washing and cleaning after filling, and further other matters necessary for operation (e.g. control parameters for equipments, movement and behavior in clean room, system for responsibility, permissible interventions).
2. Processing of sterile pharmaceutical products (e.g. filling, capping, freeze-drying) and operations where sterile containers (including stoppers) that directly contact with aseptically filtered products will be exposed to the environment, should be done in a critical area (Grade A). If vial capping is undertaken outside the critical area, vials should be protected with Grade A air supply after leaving the aseptic processing area and until the cap has been crimped completely. Crimping of vial cap should be undertaken in areas of at least Grade C taking into consideration of contamination risks due to container-closure integrity, and if necessary, additional supplementary measures should be implemented to prevent or minimize the risks of contamination during crimping by microbial and non-viable particles. The distance of the location and the duration of time between stoppering and capping should be as short as possible.
3. In aseptic filling processes, environmental monitoring should be undertaken for the full duration of critical processing, starting from preparatory stage such as assembly of filling

machines and container supply machines that would directly contact drug products, and then monitoring data obtained should be duly evaluated. The information on how to undertake environmental monitoring, such as frequency, should be referred to the Environmental Monitoring Section of this guidance.

4. Equipment surfaces that come into direct or indirect contact with sterile pharmaceutical products should be decontaminated or sterilized prior to manufacturing according to validated sterilization procedures.
5. Sterilized equipment should be preserved in validated procedures to keep sterile condition until use.
6. Connecting area of a reserve tank of sterile bulk product with filling equipment (including filling lines) should be sterilized by the SIP system in a critical area (Grade A). If connecting area cannot be sterilized by the SIP system, the following alternative method to secure sterility assurance, may be employed :
   - Containers and filling equipment should be aseptically connected in a critical area.
   - If the connection is performed in Grade B or lower environment, the connecting area and any downstream thereafter should be sterilized using the SIP system.

   These procedures may not be applied to connecting system which is proved to ensure a higher sterile assurance (e.g. commercial available sterile connectors).
7. The transfer or supply of sterile materials such as sterilized rubber closures through indirect support areas should be conducted by validated procedures that ensure to maintain the sterility of such materials. The frequency of such transfer or supply should be as minimum as possible.
8. The sterility assurance level of aseptic filling process should be verified by process simulation.
9. If the active ingredients of sterile pharmaceutical products have high potent physiologic activity or are bacteria which may carry a risk of infection, the premise and equipment must be in compliaqnce with requirements and rules stipulated in the Regulations for Buildings and Facilities of Pharmacies and the Standards for Manufacturing Control and Quality Control of Drugs, Quasi-drugs (known as “GMP Regulations”). Further, the equipment and processing areas should be inactivated and cleaned after completion of processing, if necessary . If an air circulating the filling area is to discharge outside, the air should be pre-treated by an appropriate cleaning procedure prior to discharge.
10. The maximum allowable time for filling process should be established and validated for the adequateness.

16.2 Filling of Liquid Products

Aseptic liquid filling processes should meet the following requirements:

1. Sterile bulk products should be prepared using sterile containers equipped with gas filtration filters. The filters should be tested for integrity after use.
2. The maximum allowable time should be established for preparation of sterile bulk products and the process during the preparation to the filling. The maximum allowable storage period should be specified for sterile bulk products. If a solution of bulk products is prepared in a non-sterile area and subsequently sterilized by filtration during filling processing, the steril filtration should be undertaken promptly after preparation of a bulk solution to prevent or minimize the growth of bacteria or endotoxins in the bulk solution.
3. The integrity of containers used for the preparation of sterile bulk solution and connection of the containers with filling equipment should be periodically assessed and confirmed, and the procedures for the assessment should be established. Appropriate period for replacement of the gaskets should also be established.

16.3 Powder Filling Processes

Aseptic powder filling processes should meet the following requirements:

1. Bulk powder to be filled should be stored in hermetic containers, unless an alternate method has been verified to be equivalent or more effective in keeping the powder free from contamination with foreign matter or microorganisms.
2. SOPs for assessing the integrity of hermetic containers used to store bulk powder should be established and verified. The frequency and procedures for replacing gaskets should also be established.
3. Control criteria for airborne particulates should be established f during powder filling processes in APA filling areas by taking into account the potential influence of dust on counting particulate matter. The criteria should be based on the following data obtained through validation conducted under operating conditions with the HVAC system running.
    - Particulate count determined with the powder filling machine halted
    - Particulate count determined with the powder filling machine idle
    - Particulate count determined during operation of powder filling machine (monitoring during periodic validation of process control)
4. If the outer surface of the product container is cleaned with compressed air following filling of bulk powder, the dispersion of powder into the surrounding environment should be minimized by appropriate preventive measures.

17. Filtration Sterilization Processes

17.1 Liquid Filtration Sterilization Processes

17.1.1 Selection of Filters for Sterile Liquid Filtration

Filters for sterile liquid filtration should be selected based on their physicochemical properties, biological safety profile, bacterial retentionperformance, andextractable profile, followed by the assessment of compatibility with pharmaceutical products and process characteristics such as required membrane surface areas in accordance with the assessment protocol or procedure. Generally, the nominal pore size for sterilizing filters suitable for sterile liquid filtration is less than 0.2/0.22 μm.

17.1.2 Implementation of Sterile Liquid Filtration and Process Control

Process parameters necessary for sterile liquid filtration should be established based on characteristics of filters and pharmaceutical products, and then be validated for these parameters.

1. Cleaning procedures

   The filtration system (including secondary fluid path [e.g. pipes and holding tanks set after the filter]) should be assessed for efficiency in removing extracts, insoluble particulate matter, oxidisable substances, etc.

2. Filter sterilization procedures

   A sequence should be established for filtration sterilization procedures, and these procedures should be verified to be efficient in cleaning and sterilizing without damaging the filters. The maximum cumulative time allowed for use of an individual filter under applicable sterilization conditions should be specified under conditions of repeated use. Common procedures for filter sterilization are autoclaving, gas sterilization, and radiation sterilization.

3. Filter integrity test method

   Filters used in the manufacturing process should be tested for integrity by a non-destructive method experimentally demonstrated to provide data that correlate well with data on the filter’s bacterial retention capacity. Methods of testing filter integrity include the diffusion flow (forward flow) and bubble point test. “Demonstration of correlation” means verification that a filter satisfying the integrity test limit value can maintain bacterial retention capacity (if the limit value is not exceeded, the filter is not guaranteed to have sufficient bacterial retention capacity). Basic data on filter integrity should be obtained from the filter’s manufacturer.

   (1) Filters should be wetted with suitable wetting solutions recommended by the filter’s manufacturer or products actually used for filtration sterilization.

(2) SOPs for the integrity test should include, but not be limited to, the following:

- Procedures for filter wetting
- Environmental conditions for integrity testing
- Confirmation of testing processes
- Evaluation of filter test failure and trouble shooting
- Recording of test results
- Conditions for filtration sterilization process

4. The filtration sterilization process should be validated under operating conditions, assuming the worst-case scenario, by taking into account the points listed below. Potential risks associated with aseptic processing should be assessed, and introduction of multistage filtration should be evaluated as needed. If a multistage filtration system is employed, the sterilizing filter should be placed as close as possible to the filling valve.

(1) Compatibility of filters with pharmaceutical products (e.g. chemical resistance)

(2) Maximum filtration time or maximum time of contact with pharmaceutical products

(3) Maximum filtration volume

(4) Maximum flow rate

(5) Temperature

(6) Maximum differential pressure

17.1.3 Filter Validation of Product-Specific Bacterial Retention Performance

1. Bacterial challenge test

Filters should be validated for ability to capture bacteria potentially present in individual pharmaceutical products under operating conditions, assuming the worst-case scenario, e.g. maximum filtration volume or maximum differential pressure. Filters may be validated in groups classified by properties of sterilization solution or process conditions.

2. Challenge solutions and challenge bacteria

(1) Challenge solution

The solution used in the bacterial challenge test should be a solution of pharmaceutical product which is sterilized by filtration in actual manufacturing production. If the challenge test procedures need to be modified for some reason, such as because the pharmaceutical product has bactericidal prpperty, filtration processing should first be conducted with the drug solution to be sterilized under simulated worst-case scenario conditions for actual manufacturing production in order to verify the compatibility of a

drug substance with the filter, and then the challenge test should be performed under modified test conditions.

(2) Challenge bacteria

The challenge test should be conducted with *Brevundimonas diminuta* (ATCC 19146) or other scientifically selected bacteria to confirm that the filtration process generates a sterile filtrate. The challenge level should be at least 10^7 colony-forming units (cfu) of test organism per cm^2 sample surface.

17.1.4 Routine Procedures

1. Cleaning of filtration system

   Filter housing and pipes of filtration system should be cleaned by appropriate procedures established during the process development phase of the filtration system. As a rule, filters are not generally cleaned or reused; however, if used again, filters should be cleaned via established appropriate procedures.

2. Sterilization of filtration system

   Filtration system should be sterilized promptly after completing the cleaning process by appropriate procedures established during the process development phase of the filtration system to prevent microbiological proliferation.

3. Filter integrity test

   Filters should be verified for integrity after filtration processing (after use of filters) without disassembling the entire filter. Integrity should also be confirmed prior to the filtration process (before use of filters), as appropriate, by evaluating potential risks inherent to the process.

4. Bioburden control

   Bioburden level of pharmaceutical products prior to filtration should be checked with appropriate frequency.

5. Maintenance and change control

   Appropriate procedures should be established and implemented to maintain and control filters and filtration system equipment including testing and inspection equipment. Procedures should also be established for confirmation and recording of changes to be made to the conditions for filter use and maintenance control.

6. Personnel training

   Personnel involved in filtration sterilization during manufacture should be adequately trained. Training program should include, but not be limited to, operation procedures for integrity testing, procedures and implementation of investigation into reasons for integrity test failure,

loading and unloading of filters, and cleaning and sterilization of filters.

7. Manufacturing records

Manufacturing records should include, but not be limited to, the following filtration sterilization-related information:

(1) Procedures for filtration sterilization

(2) Name and batch number of pharmaceutical products filtered

(3) Names and signatures (or seals) of operators in charge of filtration sterilization

(4) Name of filter manufacturer and types, lot numbers, and/or serial numbers of filters

(5) Cleaning and sterilization conditions for filters and filtration system

(6) Conditions of the filtration sterilization process (e.g. differential pressure, primary and secondary **side** pressure, flowrate, operating temperature, duration of filtration, processing volume)

(7) Conduct and outcome of filter integrity test

17.2 Air and Other Gases

17.2.1 Selection of Filters for Gas Filtration Sterilization

Filters for gas filtration sterilization should be selected from those made of hydrophobic materials based on their physicochemical properties, biological safety profile, and bacterial retentionperformance. The membrane surface area necessary for efficient filtration should be calculated based on flow rate and differential pressure specific to individual processes. Generally, the nominal pore size for sterilizing filters suitable for sterile air filtration is less than 0.2/0.22 μm.

17.2.2 Implementation and Control of Air Filtration Sterilization

1. Procedures for air filtration sterilization

Gas filters are generally used repeatedly. The maximum allowable cumulative time of filtration under applicable sterilization conditions should be established before use. Common procedures for filter sterilization include SIP system, steam sterilization in an autoclave, and radiation sterilization. With steam sterilization, water may be retained in the filter to possibly reduce filtration flow rate; therefore, the filter needs to be dried well but as quickly as possible to prevent bacteria proliferation.

2. Filter integrity test procedures

(1) The filter integrity test should be non-destructive and suitable for determining a filter's bacterial retention capacity (refer to Section 17.1.2 3).

(2) Processes in which filtered gas comes into direct contact with sterilized products

Air filters used in processes in which filtered gas comes into direct contact with sterile pharmaceutical products (e.g. processes using aseptic filling equipment, vent filters of sterile bulk holding tanks, freeze-drying equipment, vacuum-break filters of autoclave) should be subjected to an integrity test which provides data positively correlated to data from the bacteria challenge test performed with liquids used in testing filters for sterile liquid filtration (in general, the challenge test is conducted by the filter manufacturer using liquid [water, routinely]). Details of the filter integrity test should be confirmed with the filter manufacturer (refer to Section 17.1.3).

(3) Air filters used in processes in which filtered gas does not come into direct contact with sterilized products (e.g. air supply during bulk intermediate product manufacturing process and fermentation process) should be controlled by establishing appropriate control procedures based on risk analysis.

3. Conditions of filtration sterilization process

Gas filters are generally used repeatedly for a significant period of time. The materials of the filter should be examined for durability, including resistance to oxidation and degradation. In addition, the following parameters (1) to (5) for gas filtration sterilization should be established prior to processing. Unlike with filters for sterile liquid filtration, process parameters for gas filters cannot be realistically established by assuming the worst-case scenario; therefore, it is not absolutely required for the manufacturer to validate the bacterial retention capacity of each process.

(1) Temperature

(2) Maximum pressure differential

(3) Gas flow direction

(4) Duration of use

(5) Frequency of filter sterilization

17.2.3 Confirmation of Bacterial Retention Capacity

Bacterial retention capacity of gas filters should be confirmed by evaluating the methodology and results of the retention test documented in the filter manufacturer’s product warranty certificate and validation support data.

17.2.4 Design of Filtration System

Condensation tends to build up on filters of filtration system, leading to reduction in the flow

of filtrate and inviting proliferation of bacteria. Filtration system should be designed to remove condensed water from filters and their housings promptly upon generation. If such generation is inevitable as with the WFI tank, certain preventive measures such as heating of filter housing should be instituted (refer to Section 17.1.4).

17.2.5 Routine Procedures and Validation

If particles and fibers of gas filters may become detached and affect the quality of pharmaceutical products in processes during which filtered gas comes into direct contact with sterilized products, the detachment can be evaluated using liquids. Generally, the need for filter cleaning validation (e.g. CIP, cleaning prior to sterilization) by the drug manufacturer should be determined based on data provided by the filter manufacturer (refer to Section 17.1.4).

18. Freeze-Drying Process

18.1 General Requirements

1. Vials must remain unstoppered and ampoules unsealed in the freeze-drying process to be exposed to the environment. Appropriate measures should be established to prevent microbial contamination of pharmaceutical products during transfer from the filling area to a freeze-drying chamber, while being held in a freeze-drying chamber, or while being processed from freeze-drying to sealing.
2. Transfer of materials and products into the freeze-drying chamber should be carried out in a working area maintained at the critical area cleanliness level (Grade A). If possible, the transfer method should be one which does not require human intervention, such as tunnel-type automatic transfer lines, transportation vehicles equipped with a unidirectional airflow device, and isolators.
3. Vials freeze-dried but yet to be capped and ampoules to be heat-sealed or have caps screwed on should be processed in a pathway or working area maintained at the critical area cleanliness level (Grade A).
4. Containers and closures should be designed so as to maintain suitable air-tightness between time from capping in a freeze-drying chamber to having caps screwed on. If the screwing process is conducted in a non-aseptic processing area, the cleanliness of capped vials should be maintained by applying Grade A air until completion of cap-screwing after transfer from a critical area (Grade A). Cap-screwing should be performed in an area of Grade C or higher cleanliness, depending on the level of contamination risk anticipated given container-closure tightness requirements, and additional preventive measures should be taken depending on the level of contamination risk with microorganisms or particulate matter generated during

cap-screwing. The distance between points of cap application and cap-screwing and time between these processes should be as short as possible.

5. Microbial cleanliness level should be supervised in the areas where the operations described in Items 2), 3), and 4) above are conducted.

6. Sterility of pharmaceutical products with screwed-on caps should be ensured via the validated container/closure system integrity test and in-process control tests. All ampoules and other containers sealed by fusion should be subjected to a leak test or other test that ensures the integrity of the products after the fusion process. Vials mounted with closures for screwing should be checked for completeness of closure placement to eliminate vials with missing closures or those inappropriately stoppered. Recommended procedures to confirm the tightness of closures include close torque control and press pressure control.

7. Entry of air into processing chambers (e.g. machinery room) under reduced pressure relative to the outside environment should be strictly kept to a minimum to ensure the sterility of pharmaceutical products during the freeze-drying process. Procedures necessary for ensuring the reliability of leak tests to supervise air entry and integrity tests of vacuum break filters and leak filters to control vacuum level should be established and implemented.

18.2 Validation

1. The sterility of the freeze-drying process should be ensured by developing and validating microbiological and physical monitoring programs for the process itself and processes immediately before and after. The microbiological monitoring program is usually comprised of a media fill test, process simulation test, assessment of bioburden during sterilization (including for freeze-drying equipment for general use), and bioburden control features. The physical monitoring program is comprised of a leak test and integrity test for vacuum break filters and leak filters. Routine validation of the sterilization process, bioburden control, and filter integrity test should be conducted in a manner similar to that employed with equipment actually used in the manufacture of sterile pharmaceutical products.

2. Process simulation should be conducted in accordance with provisions stipulated in Chapter 20 as one of the critical control programs for the freeze-drying process. It is important to select appropriate conditions by referring to actual manufacturing processes in order not to inhibit the growth of bacteria nor impair the viability of culture media.

   (1) Temperature and time for cooling purpose should be appropriately specified.

   (2) Pressure reduction should be gradual so as not to cause explosive boiling or spontaneous freezing.

   (3) The freeze-drying program (particularly, drying time) should be carefully established to

avoid drying the culture media or impairing the viability of culture media.

(4) With regard to the freeze-drying processes, those processes which cause turbulence at the time of starting pressure reduction, vacuum break, or loading of materials or products to be freeze-dried, and processes with the highest risk of microbial contamination—such as a process with human intervention—should be simulated and evaluated repeatedly several times under the worst-case scenario.

(5) Some freeze-dried products need to be prepared with containers filled with inert gas such as nitrogen to ensure product stability. If growth conditions for aerobic bacteria need to be secured, air should be used instead of inert gas. If anaerobic bacteria are identified or suspected to be present in the preparation, inert gas and growth media for anaerobic bacteria should be used.

3. If the capacity of the freeze-dryer is equal to or smaller than the standard equipment with respect to accommodating the standard unit number of media, the equipment concerned should be loaded with a unit number of media suitable to the size. If the capacity of the freeze-dryer is larger than the standard (5,000 units of media), containers filled with media should be placed at appropriate locations within the freeze-drying chamber: medium containers should be randomly placed or decimated in sequential order to be evenly placed for unbiased evaluation. If the evaluation assumes the worst-case scenario—including incomplete integrity of vacuum break filters, leakage from doors or ice-condensers, or back-diffusion of gas or air from vacuum pump—medium containers should be placed in locations where the risk of contamination associated with any one of these abnormalities is particularly high.

4. The integrity of containers and closures should be validated to ensure the sterility of pharmaceutical products.

5. The validity of the leak test and the integrity of vacuum break filters and leak filters for vacuum control should be validated for the control of air entry into the freeze-dryer chamber under negative pressure. The judgment criteria for the leak test should be strictly established by taking the following factors into account so as to minimize the risk of microbial contamination within the chamber of freeze-drying equipment: volume of the freeze drying chamber, retention time under reduced pressure in the freeze-drying process, and environment surrounding the freeze-drying equipment.

18.3 Cleaning and Sterilization of Freeze-Drying Equipment

1. Cleaning of freeze-drying equipment should be scheduled after taking the following factors into account:

(1) Cleaning procedures for freeze-drying equipment should be established with due

awareness of the difficulties involved in cleaning the complex inner structure of the freeze-drying chamber.

(2) Sampling procedures for verifying cleaning efficiency should include sampling of drained rinse water and combine the swab method to sample materials at the nearmost surfaces of shelves and areas around drains. The transfer method using clean sticky tape is also an effective sampling procedure. For verification of cleaning efficiency using the rinse-water sampling and swab methods, a pharmaceutical product (actual or simulated) employed as an indicator of cleaning efficiency should be selected based on ease of cleaning and pharmacological activity of the pharmaceutical product.

(3) When a detergent is used in cleaning, toxicity and other relevant data for the agent should be obtained from the supplier for evaluation, and appropriate assessment procedures for the swab and rinse-water sampling methods should be established to assess potential effects of residual agents on pharmaceutical products to be freeze-dried.

2. Appropriate sterilization procedures should be established and validated to ensure the sterilization of freeze-drying equipment.

(1) Freeze-drying equipment has a complex inner structure and is composed of materials varying in type and size. Sterilization procedures for the equipment should therefore be sufficiently comprehensive to secure complete sterilization after taking into account possible cold spots and diffusion of sterilization gas throughout the complex chamber. In particular, with regard to sterilization procedures which use gas, temperature and humidity inevitably vary within the chamber, and therefore sterilization should be conducted over sufficient time to allow for permeation. Circulation and diffusion patterns of gas should be evaluated in detail for optimization of sterilization procedures.

(2) With regard to sterilization procedures which use steam, given the complex inner structure of the chamber, due care should be exercised to achieve efficient displacement of stagnant air and removal of condensed water.

(3) Steam sterilization should be conducted for every freeze-drying cycle, as a rule. When the interval of sterilization is changed in accordance with properties of pharmaceutical products or for other reasons, the validity of sterilization between intervals should be ensured by microbiological validation.

18.4 Routine Monitoring and Control and Maintenance of Freeze-Drying Equipment

1. The leakage of gas from freeze-drying equipment should be measured at the time points described below. Caution should be taken when identifying or measuring the volume of pseudo-leaks of gas generated inside the freeze-drying chamber.

(1) Leak test for every batch of pharmaceutical products at the completion of freeze-drying

Records of leak test data should be obtained in brief at the completion of freeze-drying.

(2) Leak test at the completion of steam sterilization

Records of leak test data should be obtained after cooling of freeze-drying equipment since steam sterilization exerts significant stress on the chamber.

(3) Leak test during periodic revalidation

Freeze-drying equipment should be run through an empty cycle overnight to measure leakage of air or gas from the equipment during periodic revalidation.

(4) An additional leak test should be conducted upon detecting actual or signs of abnormal leakage in the leak test in Items (1) or (2) above.

2. The program for periodic equipment function testing should include, but not be limited to, the functional diagnosis of the heat transfer/circulation system for shelves, the cooling system for refrigerating machines, and the vacuum/exhaust system.

3. Vacuum break filters, leak filters, gaskets for vacuum sealing, and other parts should be periodically replaced depending on their cumulative duration and frequency of use.

4. Critical instruments for monitoring and controlling freeze-drying equipment such as temperature regulators and vacuum gauges should be calibrated periodically and have their calibration results documented for records. A calibration interval of approximately 6 months is recommended unless previous calibration results suggest a need to change the interval.

5. Vacuum gauges are highly sensitive meters used to measure very minute changes in pressure, and on-site calibration via the method confirmed to be traceable is practically impossible. As such, it may be acceptable to contract out calibration to an authorized testing facility.

19. Isolator System, Barrier System, and Blow-Fill Seal

19.1 Isolator System

A properly designed isolator system provides an extremely aseptic environment but does not provide a hermetically sealed enclosure. Although highly potent pharmaceutical products with high pharmacological activities are occasionally manufactured in an isolator system with a cabinet maintained under negative pressure, sterile pharmaceutical products are usually manufactured using an isolator system operated under positive pressure. In addition, ensuring product sterility requires the establishment and the implementation of a comprehensive preventive maintenance program including maintenance and control procedures for HEPA filters, gloves, half suits, and any other design features that are intended to provide enclosure integrity.

19.1.1 General Requirements

1. The air cleanliness level of an environment where an isolator system is installed for the manufacture of sterile pharmaceutical products should be Grade D or higher.
2. Connectors combining two isolators and connection ports for input and output of aseptic materials or bulk product should be structurally designed to be suitable for maintaining the integrity of the isolator enclosures.
3. Numbers of half suits, gloves, transfer ports, and connection ports for output should be kept at a minimum in order to reduce the risk of contamination.
4. The ports on isolators such as those used to transport finished products outside the isolator, should be suitable to prevent contamination from entering the enclosure. These port openings should have adequate air flow moving from the enclosure to the surrounding environment. Generally, this is achieved by maintaining the pressure difference at an appropriate level.
5. The efficacy of decontamination process applied to the isolator enclosure and associated equipment should be verified biologically by confirming a 4 to 6 log reduction on biological indicators known to be resistant to antimicrobial agent utilized. The level of decontamination should be established based on the intended use of the isolator and bioburden requirements. Process for decontaminating materials to be transferred into the isolator should also be validated to be capable of achieving a 4 to 6 log reduction of suitable biological indicator.
6. Product contact equipment/surface should reduce surface bioburden to the possible level prior to decontamination. Procedures for decontamination product contact equipment/surfaces within the isolator will generally require 6 log or greater spore log reduction established through the use of appropriate biological indicators.
7. A periodic leak test should be performed based on the criteria predetermined for leak detection sensitivity.
8. Decontamination frequency should be established based on the level of potential risks of contamination, verified by appropriate validation studies, and reviewed at regular intervals.

19.1.2 Design of Isolator System

The isolator system should be designed after appropriate consideration of technical requirement. Design should consider isolator structural requirements, operational conditions, and risks associated with manufacturing operations performed inside the isolator.

19.1.3 HVAC System

1. The air cleanliness inside the isolator system should be Grade A.

2. The rate of air exchange in the isolator should be sufficient to prevent retention of particulate matter or contaminants and conditioning of air should enable temperature to be maintained within the predeterminedrange.
3. Air velocity and airflow patterns should be sufficient to maintain a clean environment necessary for operations within the isolator system.
4. Air in the isolator system should be circulated through a HEPA or higher-grade filter. The supply of outside air to the HVAC inlet and the isolator exhaust should also take place through a HEPA or higher-grade filter.
5. The pressure differential between the isolator and isolator room should be maintained at a minimum of 17.5 Pascals. A greater differential may be necessary depending on the type of operation, such as when half suits and gloves are used during operation. The pressure differential should be continuously monitored and recorded throughout operation, and an alarm system should be installed to warn operators of an abnormal drop in pressure.

19.1.4 Decontamination

1. The decontamination process should be established by taking the following points into account:
   (1) Cleaning and drying of the internal surface of isolator system, as required, prior to decontamination of the enclosure and equipment contained therein
   (2) Amounts of decontaminant injected into the isolator
   (3) Biological indicators (BIs)
   (4) Chemical indicators (CIs)
   (5) Temperature distribution within the isolator and in the surrounding environment
   (6) Humidity
   (7) Duration of decontamination process
   (8) Concentrations of decontaminants when using gas decontaminants
   (9) Pressure differential
   (10) Verification of a relatively uniform distribution of decontaminants within the isolator
   (11) Bioburden
2. Decontaminants should be selected based on evaluation of compatibility with the isolator’s materials of construction, type of operations to be performed inside the isolator, volume and configuration of materials brought into the isolator, and bioburden in the isolator. Possible agents for isolator decontamination include peracetic acid, ozone, chlorine dioxide, and

hydrogen peroxide.

3. Decontamination should be conducted by personnel with sufficient knowledge and understanding of the characteristics of the decontamination mist, vapor, or gas and with familiarity with the operation of the decontamination employed.
4. The residual level of the decontaminant should be confirmed to have been reduced to equal to or less than acceptance criterion value after completion of decontamination. The value should be established by considering not only the safety of factory personnel but also potential influence on product quality and subsequent processes.
5. Every batch of decontamination agent used should be analyzed before use to confirm that they meet their predetermined composition and identity.

19.1.5 Personnel Training

The education and training program on the use of the isolator system should include but not be limited to the following:

1. General requirements on aseptic processing
2. Proper utilization of gloves and half suits
3. The isolator decontamination process
4. Integrity testing for isolator equipment
5. Procedures for loading of materials and unloading of finished products
6. Operation, monitoring, and maintenance/control of isolator equipment
7. Safety handling and use of decontamination agents based on the relevant Material Safety Data Sheet (MSDS) and the known compatibility of decontaminants with the isolator equipment
8. Process-specific SOPs

19.1.6 Routine Monitoring and Control

Routine control requirements for the isolator system should include, but not be limited to, the following:

1. SOPs for the operation of the isolator system should be developed based onvalidated processing conditions.
2. While the isolator system is assumed to be maintained at a high level of integrity, its maintenance is not absolutely perfect. Therefore, a leak test should be performed at periodic intervals and also prior to each decontamination. Methods to be used in the leak test should include but not be limited to the following:

(1) Pressure hold test

(2) Gas detection method

3. Glove material should be resistant to all chemicals and decontaminants to be used.
4. Gloves should be checked visually for damage such as puncture or tears before each use.
5. In operations performed with gloves, gloves should preferably be supplemented by inner gloves worn beneath the isolator gloves.
6. Gloves should preferably be tested for physical leaks and subjected to microbiological monitoring using swabbing or other methods at regular intervals.
7. A maintenance and control program should be developed for consumable materials and items to specify a suitable time interval for replacement.
8. Prior to decontamination, parameters that may affect decontamination efficacy —such as temperature, humidity, gas concentration, etc.—should be monitored at predetermined locations and the results should be recorded for each decontamination cycle.
9. The total particulate count in the isolator should be monitored at predetermined locations at suitable time intervals.
10. Microbiological monitoring should be conducted at suitable time intervals at locations predetermined based on potential contamination risk in relation to structural characteristics of isolator system and properties of operations to be performed in the system. Typical example locations for monitoring include the inner surface of the isolator, glove surface, materials carried into the isolator, and material contact surfaces. The validity of the locations and frequency of monitoring must be verified at regular intervals.

19.2 Restricted Access Barrier System (RABS)

A restricted access barrier system (RABS) is a means to produce sterile pharmaceutical products by separating personnel from critical areas and minimizing direct human intervention in critical areas during aseptic processing.

The RABS is an integrated aseptic processing system to be implemented in aseptic processing areas (critical areas) comprising both hardware and software components, such as physical partitions, air supplied through HEPA filters, and appropriate operational procedures.

The structure and composition of the RABS are varied from a hard wall to a structure with tight barriers and a high degree of isolation like isolator. The HVAC system accompanying the RABS is also not uniform: the HVAC system either utilizes the air conditioning system originally available with the RABS or is an independent HVAC system. This chapter describes basic requirements specific to the design and operations of the RABS.

19.2.1 General Requirements

The RABS should be designed by taking into account the following matters as general requirements:

1. The inner environment and HVAC system for the RABS should meet the following requirements for the critical area, as stated in Chapter 7 of this document.
2. The area or room where the RABS is installed should be defined as a direct support area and the air cleanliness level in the area or room should be Grade B or higher.
3. Interventions by factory personnel, if required, should be conducted through sealed gloves or half suits. Appropriate procedures for disinfection, inspection, and replacement of gloves or half suits should be instituted and implemented to minimize risks of product contamination. Refer to “Isolator System” in Section 19.1 for detailed requirements regarding glove use.
4. The inner surface of the RABS that comes into direct contact with pharmaceutical products should preferably be disinfected with the SIP system. Parts of the surface that cannot be treated by the SIP system should be disassembled and disinfected by autoclaving or other methods and then assembled. Further, if equipment such as an isolator can be decontaminated, the surfaces of such equipment that come into direct contact with pharmaceutical products can then achieve still higher levels of microbacterial cleanliness.
5. The inner surfaces of the RABS that do not come into direct contact with pharmaceutical products should be disinfected via appropriate methods of disinfection.
6. When sterile materials need to be carried into the RABS, a transfer system resistant to contamination should be employed. If sterile materials in containers are carried into the system, the surface of the containers should be adequately decontaminated prior to the transfer.
7. When human intervention is required during processing while keeping the RABS door open, the following points to consider should be taken into account to reduce risk of product contamination:
   (1) The inside of the RABS should be appropriately disinfected after intervention to eliminate potential product contamination.
   (2) SOPs for handling containers present in the RABS at door opening should be established in advance based on potential risks of product contamination. If the door needs to be opened for an unexpected reason, all containers present in the system should be removed from the system, as a rule.
   (3) Intervention procedures should be thoroughly recorded.
8. If the door might be opened during aseptic processing, an ISO 5 (at least, no-load level)

protection booth should be installed outside the system. Air should be ensured to run from inside the RABS to the protection booth upon opening the door.

19.2.2 Personnel Training

The education and training program on the use of the RABS should cover but not be limited to the following:

1. General requirements on aseptic processing
2. Proper handling procedures for gloves and half suits
3. Procedures for decontaminating the inside of the RABS
4. Procedures for loading and unloading materials and intermediate products
5. Details on operation, monitoring, measurement, and maintenance/control of the RABS
6. Procedures for intervention while the door is kept open and relevant points to consider

19.3 Blow-Fill-Seal (BFS) System

The blow-fill-seal (BFS) system is a specialized aseptic packaging technology used in the manufacture of sterile pharmaceutical products which uses in-line forming, filling, and sealing of sterile plastic containers. Since plastic containers are molded from plastic pellets, filled, and sealed by fusion in a continuous production run under a closed and sterile environment without human intervention during the filling process, the sterility of pharmaceutical products can be ensured without terminal sterilization processing (e.g. autoclaving) after sealing. As operations are carried out as a closed, automatic, and continuous process, the BFS system features a relatively low chance of contamination during production. However, the system type varies: one type permits filling and closure in a perfectly closed system, while another requires caps and inner plugs to be supplied from outside. A sterility control program should therefore be established based on features of each system.

19.3.1 Scope of Blow-Fill-Seal System and Processes to be Addressed

Among the manufacturing processes for sterile pharmaceutical products to be manufactured using the BFS system, this guidance document is applicable to those processes not requiring sterilization (e.g. autoclaving) following filling and fusion-sealing processes. In the manufacture of liquid pharmaceutical products, the BFS system is applied to processes involving sterilized filtration of drug solution, loading of plastic pellets, molding of containers, filling of drug solution into containers, and sealing of containers. In the manufacture of powder pharmaceutical products, the system is applied to processes involving loading of sterile bulk powder, loading of plastic pellets, molding of containers, filling of the sterile powder into containers, and sealing of containers.

Particular attention should be paid to the following:

1. Elution of plasticizers, additives, and unpolimerized monomers, etc. from plastic containers
2. Pyrogenicity of plastic pellets
3. Environmental conditions for plastic container molding
4. Sterilization of drug solution (preparation of drug solution by filtration sterilization)
5. Compatibility of containers with drug solution
6. Cleanliness level of the filling environment and environment where the equipment is installed
7. Fusion-sealing operations

It is critical to establish strict criteria for the above items 2), 3), 6), 7), and "assessment of sterility" from a sterility control point of view.

19.3.2 Process Flow and Environments for Container Molding and Filling

1. Critical processes of the BFS system
   (1) Preparation of drug solution
   (2) Filtration sterilization
   (3) Temporary storage of filtered drug solution
   (4) Molding (including clean air supplied into the molding environment)
   (5) Filling
   (6) Fusion sealing
2. Characteristics of BFS processes
   (1) All processes of the BFS system from molding of plastic containers to filling and fusion-sealing should be performed in a continuous automatic operation.
   (2) Filling and fusion-sealing operations are carried out in a restricted, isolated area; therefore, the working space is not necessarily an aseptic area with air cleanliness grade of "A" which is routinely required for the manufacture of sterile pharmaceutical products. As such, it is acceptable to maintain Grade A cleanliness level only for the restricted processing areas of molding and filling. For this reason, however, accurately controlling the cleanliness level of the molding and filling areas is quite important for protecting pharmaceutical products from contamination by foreign and particulate matter.

19.3.3 Sterility Assurance of Plastic Containers

The inner surfaces of plastic containers molded by the BFS system must be sterile. Sterility assurance for these surfaces requires the following actions be implemented:

1. The quality of plastic pellets should be adequately controlled throughout the storage period to prevent excessive microbial contamination that may affect sterility and pyrogenicity of pharmaceutical products.
2. Temperature and time are key factors for not only efficiently melting and molding of plastic pellets but also eradicating microorganisms present on the pellets. Temperature and time established for processes from melting to molding need to be verified and controlled to be suitable for dry heat sterilization (plastic pellet melting and molding processes are conducted under dry-heat conditions, free from moisture).

   Note: The Japanese Pharmacopoeia recommends the use of Bacillus atrophaeus as an indicator for dry heat sterilization. The D160 value for B. atrophaeus ATCC 9372 has been reported to be 0.89 – 1.22 on glass plates and 1.22 – 2.07 on plastic plates.
3. The sterility of the molding and filling processes should be verified by process simulation.

19.3.4 Critical Control Parameters of the BFS Process

The following are critical control parameters of the BFS process:

1. Bioburden of plastics

   Bioburden (in particular, fungi) of plastic materials and additives thereof should be determined prior to use. If the plastic supplier fails to provide sufficient information on these materials, the cleanliness level of the plastic should be closely supervised throughout the manufacturing process to maintain adequate bioburden control.
2. The temperature for melting plastic pellets and the time from melting to extrusion for blow molding should be monitored and controlled at respective predetermined optimal levels.
3. The equipment for the preparation and transportation of the drug solution should preferably be designed to be adaptable to the CIP and SIP systems to ensure proper disinfection of drug solution preparation processes and sterility of pharmaceutical products. If the equipment is not adaptable to these systems, certain off-line control systems should be in place to ensure cleanliness and sterility levels similar to those achieved by the CIP and SIP systems.
4. Quality of environment air

   In the BFS system, pharmaceutical products are exposed to environment air only during molding and filling processes. Local environments for these processes and air supplied to these processing areas should therefore be monitored to maintain a Grade A air cleanliness

level, and the quality of air surrounding the equipment should be of Grade C or higher cleanliness. Operators should wear gowns suitable for these cleanliness levels.

5. Quality of air for extrusion blow molding and integrity of air filters

   Air contacting the inner surface of the container should be supplied after passing through sterilizing filters. When compressed air is used instead, the oil and water content in the air must be strictly controlled. The cleanliness level based on viable bacterial and particulate matter counts should be Grade A equivalent.

6. Air supply to local spaces for filling operations

   Air supplied to local spaces for filling operations, which are air-shower rooms equipped with a filling nozzle and parisons where melted plastic resin is inflated to form the container, is generally passed through sterilizing filters. Environmental monitoring of these local spaces is usually performed by measuring airborne particle matter. If the spaces are purged with sterile air supplied through sterilizing filters, the filter integrity test may be employed instead of particulate matter monitoring as a means to ensure air sterility. Additional environmental monitoring is necessary if filling operations in these spaces require human intervention to prepare materials for filling, adjust materials and equipment during operation, or clean up equipment.

7. Heat transfer medium and product quality

   Although the heat transfer medium is unlikely to come into direct contact with the molded plastic containers, the possibility of leakage or contamination of the medium into melted plastic should not be ruled out.

8. Integrity of fusion-sealing performance

   The integrity of sealing performance is a highly critical process parameter for the BFS system, and a number of methods—including rare gas leak and high voltage leak detection—have been developed to test the integrity. Seal integrity should be ensured via an appropriate method, and validity of the method should be verified after employment.

9. The CIP and SIP of the BFS process (temperature, time, and F_0)

10. The integrity of the SIP in the filling process and maintenance of sterility

11. Challenge test of fusion-sealing process

12. Media fill process simulation test of filling process

13. Continuous operation (acceptability of continuous operation and verification of the maximum allowable time of operation)

    The BFS process is often operated continuously with no break; therefore, the maximum time allowed for continuous operation should be established depending on stability of the drug

solution in question and microbial contamination risk over the entire process. Procedures and control parameters should be specified for resuming processing after interruption or discontinuation of operation.

20. Process Simulation

20.1 Outline and Scope

Process simulation is a technique of applying the “media fill test” concept to all aseptic processes. Sterile pharmaceutical products are manufactured by complex processing requiring handling of sterile bulk materials and other raw materials as well as multiple aseptic processes. Aseptic filling is only one of these processes involved in sterile pharmaceutical product manufacturing. The validity and reliability of the method employed for sterility assurance of pharmaceutical products manufactured by aseptic processing should be verified by validating all processes involved in aseptic processing. Process simulation is a validation method using microbiological growth media or a substance that supports microbiological growth in place of active pharmaceutical ingredients to assess not only the performance of aseptic filling process but also that of the overall aseptic manufacturing process for sterile pharmaceutical products. This process simulation is applied to the assessment of manufacturing processes for sterile API including filtration, crystallization, drying, milling, mixing, and freeze-drying on trays to obtain a powder and also overall manufacturing processes for finished sterile pharmaceutical products such as filling and sealing. Process simulation should be designed to emulate the routine production process as closely as possible, including personnel movement, working environment, and manufacturing activities and operations, under “practical” but worst-case conditions. Before proceeding with actual implementation of process simulation, the “Media Fill Test (Process Simulation)” in the General Information section of the Japanese Pharmacopoeia should be referenced.

20.2 Process Simulation Procedures

20.2.1 Frequency of Process Simulation

1. Initial process simulation

   Materials subject to initial process simulation are equipment, instruments, processes, containers of different design (except for containers different in size but same in design), etc. to be used for the first time in manufacture. Based on reference information contained in the Japanese Pharmacopoeia, media fill test should be conducted using a sufficient number of liquid products filled in containers that adequately reflect the actual filling line of one production run, with at least three replicate runs on separate days. If the product is bulk product, the test should be conducted using one production unit amount of the bulk product.

2. Repeated process simulation

Based on reference information contained in the Japanese Pharmacopoeia, process simulation should be repeated at periodical intervals of at least 6 months on each working shift for every aseptic process and every filling line, using liquid products in containers in a sufficient number that adequately represents the actual aseptic and filling operations. If the product is bulk powder, the test should be conducted using one unit production amount of the bulk product. Personnel assigned to critical aseptic processing should be trained on aseptic processing operations and take part in process simulations at least once a year.

When an aseptic process or filling line has not been used for over 6 months, process simulation should be conducted with a frequency similar to that of the initial process simulation prior to resumption of use.

Process simulation should also be conducted with a frequency similar to that of the initial process simulation prior to reuse, as appropriate, if any process, facility, or equipment is significantly modified to affect the level of sterility assurance, if personnel assigned to critical aseptic processing are changed, if results of environmental bacterial tests are not acceptable, or if sterility testing of finished products identifies contaminated products.

20.2.2 Medium Selection and Performance Testing

Process simulation should use soybean-casein digest medium or other media suitable for testing bacterial growth. If the product is bulk powder, surrogate media (e.g. lactose, D-mannitol, polyethylene glycol, powder medium) sterilized by radiation should be used instead. Details on growth promotion tests of media to be used and bacterial growth inhibitory activity assays of surrogate media should be referenced in the Japanese Pharmacopoeia.

20.3 Points to Consider for Process Simulation

Process simulation should be performed for all manufacturing processes, equipment, and operational activities that may be correlated with sterility assurance of pharmaceutical products. The key points to consider are as follows:

1. Cleaning of facilities and equipment and cleaning and disinfection of manufacturing equipment, containers, closures, and trays should be conducted in accordance with SOPs.
2. Process simulation should be performed for all routine activities at different manufacturing stages and temporal processing interventions.
3. Process simulation for temporal processing interventions which are known to occur on a routine basis (e.g. weight adjustment and supply of sterile materials, containers, closures,

environmental monitoring) and anticipated but non-programmed interventions (e.g. modification of manufacturing line, adjustment of equipment conditions, repair or replacement of equipment parts) should be performed under practical operating conditions that simulate the worst possible intervention conditions.

4. Process simulation should be performed under equipment operating conditions (e.g. lines speed) that would most likely cause contamination.
5. Process simulation should be performed over the time period determined by taking the longest possible time of actual operations into account.
6. All personnel engaged in aseptic processing are required to participate in process simulation. The simulation test should be designed by simulating the largest possible number of participating personnel and working shifts.
7. Enough medium should be filled in the container to allow the medium to contact the entire inside surface of the container on rotation or inversion, thereby rendering a reliable judgment of bacterial growth.
8. Even if inert gas is not routinely used in manufacturing, process simulation should be performed by replacing inert gas with air unless the simulation test is not intended for anaerobic growth.

20.4 Incubation and Inspection of Media Fill Units

1. If there is leakage of contents from the container or damage to the container prior to incubation, these findings should be recorded and the media fill units of concern removed from the simulation test.
2. The medium should contact all container surfaces on rotation or inversion of the container.
3. Media should be incubated for at least 14 days at a predetermined temperature within a preferred range of 20 to 35°C. If the test temperature does not fall within this range, the temperature should be justified and be within ± 2.5°C of the predetermined temperature.
4. If two different temperatures are employed in the test, the media should be incubated for at least 7 days at the lower temperature and then for the same duration at the higher temperature.
5. Growth of microorganisms should be observed on the last day of incubation when determining the absence or presence of growth.
6. If microorganisms are found to have contaminated test materials, they should be identified and characterized to clarify the causes of contamination.

20.5 Acceptance Criteria for Process Simulation

The acceptance criteria for process simulation should be consistent with those stipulated in the "Media Fill Test" listed in the General Information section of the Japanese Pharmacopoeia. If process simulation provides positive results indicating contamination, necessary actions should be taken in accordance with the Japanese Pharmacopoeia.

20.6 Process Simulation of Manufacturing Lines Equipped with Isolator System

Process simulation of a manufacturing line equipped with an isolator system may be performed with reduced frequency compared with that for a non-isolator system, provided the line has passed the initial performance qualification test, meets the conditions described below, and can be verified to have a low risk of bacterial contamination.

1. Manufacturing lines are structurally designed to completely separate the environment where personnel engage in operations from the environment where pharmaceutical products are exposed, and personnel can directly intervene only through barriers and gloves.
2. Risk management of the isolator system is performed using reliable technologies and with frequency suitable to individual control parameters (e.g. gloves, pressure difference, reverse current from the opening, loading and unloading operations, effects of cool zones in the sterilization tunnel, decontamination).
3. HVAC system, surfaces of equipment and devices that come to contact with drug solutions, filter performance, and other factors that comprise the sterility of pharmaceutical products are separately evaluated and verified to be sterile by appropriate validation and periodic reevaluation.

Annexes

A1. Active Pharmaceutical Ingredients (APIs) Manufactured via Cell Culture/Fermentation

A1.1 General Requirements

This section addresses the specific control of active pharmaceutical ingredients (APIs) manufactured by cell culture or fermentation to supplement API-related regulations, guidelines, guidance, and the main text of this guidance document.

1. The term “classical process” refers to manufacturing processes using microorganisms and cells which exist in nature or those modified by conventional methods employed from the old days. The term “biotechnological process” refers to manufacturing processes using cells and microorganisms derived or modified by recombinant DNA, hybridoma, or other biotechnological manipulation. The degree of control for microorganism in biotechnological process is usually greater than that for classical process to produce proteins or polypeptides. If natural human or animal cells are used for classical process, special precautions should be taken against potential contamination of such cells with microorganisms and viruses derived from the original human or animal cells.
2. Raw materials (e.g. (culture) media, buffer components) used in the production of APIs by cell culture or fermentation may serve as good nutrients for microbes contaminated, so that adequate control parameters, such as control of bioburden levels should be developed and implemented, taking into account the supplier information and its preparation method for raw materials, and type and characteristics of the final sterile pharmaceutical products and its manufacturing processes. Media or other materials used in cell culture should also be managed to control *Mycoplasma* and other microorganism levels, as appropriate.
3. The cleanliness level of cell culture/fermentation processing areas should be designed and controlled depending on the type of operations performed in the areas. The processing area may not necessarily be designated as a critical area, if the equipment installed in the area is a closed system. However, an adequate cleanliness level should be established and maintained to prevent contamination.
4. Preventive and safety measures against potential viral contamination in the manufacture of APIs should be implemented pursuant to ICH guideline Q5A “Quality of Biotechnological/Biological Products: Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin.”
5. With regard to in-process control and quality control (including monitoring of critical processes), the records for sterilization of the equipment, environmental microorganisms

monitoring, and all deviations thereof should be prepared and maintained to adequately control environmental microorganism level.

6. For appropriate environment control of cell culture or fermentation processing areas, the criteria for hygiene control for restriction of personnel entry, gowning, and operators health should be established and reduced to training, as appropriate.

A1.2 Cell Culture and Fermentation

In order to prevent viral or microbial contamination, working cell banks and other starting materials used in the cell culture or fermentation should be subjected to characteristic analyses and evaluation for viral and microbial safety every time they are prepared. Based on such data, contamination preventive measurements or procedures should be established and implemented to use them in the manufacturing.

2. Where aseptic addition of cell substrates, media, buffer, and gases is need in a closed or open system, the equipment should be selected to achieve sterility assurance and containment condition. If inoculation into the culturing vessels, transfer of the cultures thereafter and/or additions of media or buffer is to be necessary, an adequate operating control and procedures should be established to minimize the contamination risk.
3. Critical process control parameters (e.g. pH, temperature, dissolved oxygen) and productivity (yield) should be monitored. If any unusual results are noted in these parameters, the possibility of contamination with bacterial, fungal, or *Mycoplasma* should be assessed.
4. If the cell culture or fermentation is performed with continuous culturing apparatuses like a perfusion system, which is designed to continuously feed media and discharge culture solution from the vessel, an appropriate operating procedure should be established to ensure that cell culture can be continuously performed throughout the culturing period, without any unwanted influence to product quality, like contamination.
5. Equipment used in cell culture and fermentation should be cleaned and sterilized after every use. Fermentation equipment used in classical process should be cleaned and disinfected appropriately. When genetically engineered microorganisms or cells are to be transferred (or disposed) outside from the biological safety management areas, the transfer should be started only after inactivation of such microorganism or cells is performed by a validated procedure, as stipulated in the Law Concerning the Conservation and Sustainable Use of Biological Diversity Through Regulations on the Use of Living Modified Organisms (the Cartagena Law), and completion of inactivation should be confirmed every time before transfer. Washing of cell culture and fermentation equipment should be performed by a validated cleaning procedures established by taking into account the characteristics of the materials to be washed

off. In addition to CIP and SIP, other cleaning methods such as cleaning with complete disassembly and manual cleaning should be conducted, as appropriate, depending on the structural characteristics of the equipment.

6. Culture media should be sterilized before use via a method suitable for protecting the quality of culture solution or fermentation solution.
7. Standard procedures for counter-measurements in the event of contamination with bacteria or others (e.g. decontamination, disposal, washing feasibility check, potential impact on finished products) should be established.
8. The process for seeding and additive addition should be basically performed in a closed system. If these processes are to be performed using open vessels, it should be conducted in a biosafety cabinet or similarly well-controlled environment to prevent contamination. These measures should be controlled to prevent contamination from personnel, environment, and production process.

A1.3 Harvesting, Isolation, and Purification

1. Cell harvesting to either remove cells or cellular components or recover cellular components after cell disruption should be performed in an area and with equipment that are designed to minimize the risk of microbial contamination of the harvested material, as well as the risk of environment and personnel.
2. If an open system is used in the purification process, purification should be performed under well-controlled, clean environment conditions suitable for maintaining the quality of intermediates purified.
3. Removal or inactivation of microorganisms, cells, cellular debris, and media components should be conducted under conditions suitable for minimizing risk of API quality deficiency due to degradation, contamination, or other causes.
4. Buffers, column chromatography apparatus, and other materials used for the purification process are not necessarily required to be sterile; however, the microorganisms level should be controlled not to make any influence to the product quality. If purification and column chromatography equipment cannot be sterilized, it should be decontaminated with a suitable organic or alkaline solution. As bioburden level may vary depending on the type of process, operation time, buffer solution, temperature, pH, etc., the control level should be established for individual processes and conditions involved in manufacturing. If the process cannot be sterilized, the level of endotoxins should be measured as a part of in process control, and appropriate endotoxin control levels should be established to detect the increase of endotoxins beyond the control level.

5. All equipment should be properly cleaned after use and, if appropriate, disinfected, , or sterilized, whenever feasible.
6. Purified API and intermediate products should be stored under predetermined appropriate conditions, such as sterilization by filtration or other appropriate methods.

A2 Pharmaceutical Water

Basic concepts applicable to the manufacturing control and quality control of pharmaceutical water are indicated as follows.

A2.1 Considerable Points Essential to~~r~~ Basic Design of Pharmaceutical Water Equipment

The basic design of the equipment~~,~~ and other subsystems ~~s~~ applicable to pharmaceutical water production should be developed after establishing the procedures necessary for the efficient manufacturing and quality control of pharmaceutical water so well as to maintain ~~a~~ constant supply of pharmaceutical water in required quality. Critical points to consider on designing the water systems should include, but not limited to, the following:

1. All of the grades, specifications, quantities, and control methods for pharmaceutical water(s) should clearly be defined.
2. The variant quality of source water including seasonal changes ~~y~~ should ~~be~~ thoroughly be ascertained.
3. The principal water system design should be predetermined on maximum momentary water flow rate, application time and frequency of water to be used, and such conditions demanded at the points of use as temperature, number of ports, and piping specifications~~,~~ including branches and pipes' diameters.
4. Pharmaceutical water equipment should have such a reliable sterilization or sanitization system as to ensure microbial control provided.
5. The locational adequacy of water sampling ports for water quality control should be evaluated so well as to ensure stable supply of pharmaceutical water that fulfill required quality specifications. Water samples should be collected from the locations not only of points of use but also other critical points for the pharmaceutical water process. Locations necessary for water quality assessment should be provided with certain structural features that facilitate the sampling for quality analysis. If no sampling ports can structurally be set up at the expected locations, the ports should preferably be located as close to the points of use as possible.
6. Although the water supply to the points of use should in principle be made through a loop system, any appropriate alternative means for maintaining water quality should be employed,

when water circulation is inapplicable ~~s~~. No filters should be placed at any downstream locations in the water purification system from the viewpoint of potential risk free from microbial growth. However, filters may be placed at some upstream points of the water purification system to eliminate impurities (e.g. with a protective filter attached to the outlet of activated carbon filtration system).

7. Any backflow of water from the points of use should be prevented in consideration of such appropriate procedural and mechanical steps as to adjust the pressure differences and to regulate the valves.
8. Member materials used for pharmaceutical water equipment should be selected so suitably as to maintain and control water quality at the required level. In particular, such corrosion-resistant materials as AISI stainless steel 316 grade should be selected and have smooth surfaces given especially at the locations contacting water for injection (WFI). The surfaces subject to sterilization with pure steam or high-temperature water circulation should preferably be finished by means of passivation.
9. The entire piping in the high-purity quality water system should be installed at such an angle as to allow complete and easy drainage of water from the system.
10. As water will readily stagnate at “dead legs” occurring in T-shaped branches from the main piping leading thence to a closure mechanism such as valves, the distance between the diametrical axial center of the main piping and the closure mechanism in use should not be longer than six times to the inner diameter of the branch, but desirably not longer than three times if possible.
11. Measuring instruments should be a sanitary type free of water stagnation.
12. The directions and contents of fluids running through the various installed pipes should be displayed on the outer surfaces of the piping at locations accessible to operators at an appropriate interval.

A2.1.1 Pretreatment Equipment

Pretreatment equipment should be selected in consideration of the capacity suitable for maintaining invariable water quality within the specifications required and for maximizing water treatment efficiency and system life on the basis of elaborate investigation of the amounts of heavy metals, free chlorine, organic matter, microorganisms, and colloidal particles, etc. present in the source water.

A2.1.2 Equipment for Producing Water for Injection

The manufacturing equipment for water for injection should be designed so as to facilitate periodic

sterilization with pure steam. If steam sterilization is inapplicable to the equipment because of its low heat resistance, an alternative system should be allowed to perform sterilization or sanitization using hot water or chemical agents. Some points to consider in designing the equipment for producing WFI are summarized below.

1. Distillation Equipment (Water Stills)

Commonly applied types of distillation are single-effect, multi-effects, and vapor-compressors. The latter two types are so highly efficient in producing high-quality water and highly energy-saving as to be recommended for a large-scale of pharmaceutical water production. Since each of these three methods has different attributes, it is important to select a proper distillation method based on the intended use, and the estimated fuel consumption in order to fully utilize the advantages of each method.

The design of the water distillation system should include such adequate and practical considerations as to satisfy the specifications required for the still combined with the procedures of such feed water pretreatment as ion-exchange, reverse osmosis, ultrafiltration, and any other subsystem used and to prevent any entrainment of impurities carried over with vapor and to determine a blow-down flow appropriate for prevention from scaling due to condensation.

2. Reverse Osmosis (RO)

The reverse osmosis (RO) is used to improve various factors in water quality by allowing water to flow through permeable and semipermeable membranes based on osmotic pressure differentials to remove small molecular solutes similar in size to inorganic salts as well as solvent molecules, microorganisms, endotoxins, etc. depending on their respective concentrations in source water. Although RO can be treated at an ambient temperature and its performance is highly cost effective in energy-saving compared with distillation, stricter control than that of distillation is required to prevent any leaks due to pinholes into the downstream and microbial contamination. Points to consider in designing RO membrane units are shown below:

(1) As no gaseous carbon dioxide and ammonia can be removed from feed water by RO, such prior pretreatment as deaeration, neutralization, and/or ion-exchange should be required on occasional demand.

(2) Appropriate equipment for the microbiological control and monitoring should be included in place in the pretreatment system for feed water to meet the predetermined control criteria.

(3) As RO generally operated at an ambient temperature may cause some concern about

downstream contamination due to leaks through pinholes developed in the membrane, the structural system composed of two ROs in series should preferentially be designed to provide enhanced reliability and better control. Additionally, UV sterilization, heat-sterilization, and other appropriate treatments in the downstream should be performed to inhibit microbial growth in the system

3. Ultrafiltration (UF)

Ultrafiltration (UF) is a hyper-filtration method capable of removing endotoxins from feed water. Unlike RO systems, UF units can generally be operated at a far lower pressure than RO and are excellent in heat-resistance. Some UF membranes are made of materials resistant to steam sterilization, and hence the membranes can ~~be~~ relatively allow their surfaces to be easily sterilized with high-temperature water or chemical agents. It is recommended to select high-grade UF membranes capable of removing organic substances with a molecular weight of fraction exceeding 6,000 Daltons and suitable for the intended use. Although the purification performance of UF modules is dependent on the upstream water quality and the modules' grade as that of RO, routine maintenance and control of the UF system should be made in order to exercise no ill effects on the purification performance and water quality developed by microbial growth due to the fouling of particulate matter and microorganisms.

4. Storage Tanks for Water for Injection (WFI) and Other High-purity Waters

WFI should preferably be used so immediately after production as to avoid any intermixture contamination with microorganisms and other chemical substances. The following factors should be taken into account in storing WFI and other high-purity pharmaceutical waters in tanks.

(1) Storage tanks should be a closed-type with smooth inner surfaces. The nozzles of a level indicator attached to the tank should be minimum in number and as short as possible.

(2) Storage tanks should be structured to allow no water stagnation and easier cleaning of the inner surfaces and to facilitate~~s~~ complete drainage.

(3) The appropriate capacity of a storage tank should be determined to provide a water turnover at the highest possible rate. However, wherever feasible, a longer storage of pharmaceutical water in the tank should be avoided. The maximum storage time should be established by validation.

(4) The storage tank should be provided with such a hydrophobic ventfilter with micropores of 0.2 or 0.22 μm as to prevent the tank from any invasion of microorganisms and foreign

matter. The integrity of the ventfilter should be ensured prior to installation and at regular intervals thereafter.

(5) Where hot water is supplied into a storage tank, a heater should preferably be set up around a vent filter to prevent the filter from obstruction due to condensation of the hot water.

(6) When the tank is disinfected with hot water, the tank should be equipped with such an additional mechanism as to have heat spread over the whole inner surface of the tank including its upper part.

(7) As common safety valves are difficult to disinfect or sterilize because of their structural complexity, a sanitary type of safety valves should be employed or combined with a rupture disc type of valve to ensure the water quality in the tank. When a rupture disc valve is used, an alarm system should desirably be in place employed to give an alarm signal on the rupture.

(8) As the gas-liquid interface in a tank is a part ready to induce microbial growth and develop corrosion, water should preferably be spread over throughout the entire tank~~,~~ including the tank top with constant water fluidity kept.

5. Piping Structure

Pharmaceutical water stored in a tank is transported to the points of use through the piping with relatively small diameters and structured as a closed system so that the inner situation of the piping, once installed, is difficult to examine and inspect . Therefore, thorough review of control methods and preventive measures for troubles in the piping system should be made at the design phase. Key points to consider in the piping system are described below:

(1) It is basically preferable that the piping system should not be provided as allowable as possible with any bypass or branch through which water is not constantly running.

(2) WFI should preferably be circulated constantly at a temperature not lower than 80°C and at a turbulent flow rate enough to prevent microorganisms and organic matter from anchoring on the surfaces. Where no water circulation is given, the unused water should be drained and refilled with new water.

(3) Any loop circulated at an ambient temperatur should be considered on some preventive measures for microbial growth. One example is the employment of UV lamps (Germicidal Ultraviolet Lamp) placed at an appropriate location along the piping route.

(4) ~~If~~ The piping system ~~is~~ designed as a closed-loop should be provided with some preventive measures in the loop to maintain a positive inner pressure against any backflow

from points of use.

(5) Where no circulation system is adopted, the system should be provided with such preventive measures as hot water flushing or steam sterilization for microbial contamination prior to water supply.

(6) Every horizontally arranged piping should have an inclination of at least 1/100 given to prevent water from stagnation in the piping in drainage and steam or hot water sterilization .

(7) The piping system should be provided with an ejection port allowing for adequate and easy drainage and designed to prevent backflow.

(8) Special considerations should be taken to eliminate any risks of cross contamination at the shutdown, in abnormality, in maintenance and check of the system relating to the piping of supply water used for manufacturing pharmaceutical products which quickly disperse into the air to induce hypersensitive reactions in minute amounts or such products that may have significant effect on the attributes of other products upon cross contamination. The separate piping route for different products should be arranged in the other exclusive system. If a single system is inevitably used in the manufacture of different products, such efficient measures should be implemented as to prevent or minimize cross contamination.

6. Heat Exchangers

Any contamination of feed water due to the leakage of heat medium contained in the heat exchanger should be prevented. A double tube type or a double tube-sheet type (shell-and-tube type) of heat exchanger is generally used. Any plate-type of heat exchangers should not be used for manufacturing WFI. When ~~If~~ a heat exchanger other than the first two types is used, a heat exchanger allowing no contamination of feed water due to heat medium should be selected. If any potential risk of contamination of feed water is supposed, a positive pressure on the feed water side should be maintained at a level higher than that on the heat medium side, and an appropriate monitor~~ing~~ system and alarm for the pressure differential should be attached to the heat exchanger.

7. Points of Use and Sampling Points

Adequate design and control of the points of use and sampling points should be made in consideration of the following:

(1) No sterilizing filters should in principle ~~not~~ be placed at any points of use, since the

filters may hamper adequate monitoring of microbiological contamination in the water system and endotoxins could be released from microorganisms retained by the filters or from dead microorganisms in the filters. If the attachment of sterilizing filters is unavoidable, the frequency of disinfection/sterilization and replacement should be determined based on validation. No sterilizing filters should preferably ~~not~~ be placed in the loop for water supply.

(2) When no water samples can be collected at the points of use, sampling ports should be installed as close to the points of use as possible, except for the cases where the sampling and/or the installation of such sampling ports are regarded to be obviously disadvantageous.

(3) Sampling locations should be structured to have neither influence of initial blow-down prior to sampling nor limitation of sampling containers.

8. Valves and Instruments

Diaphragm valves, instruments, detectors, etc. mounted on the pharmaceutical water system should be free from water stagnation or dead spaces. Valves should be designed to achieve sanitary application. Electric conductivity meters and total organic carbon (TOC) meters should preferably be installed in the in-line in order to monitor chemical quality of water in a timely manner. The locations of these instruments should be selected at the points that best represent a local water quality in the piping system.

9. Pumps

Pumps should be a sanitary type in structure of a sealed casing protected against contamination and be capable of withstanding hot water sanitization and/or pure steam sterilization. Although centrifugal pumps made with stainless steel are mostly used, some appropriate pumps should preferably be selected from the viewpoint of such key functions as a head, discharge capacity, contact surface smoothness, and mechanical seal integrity in consideration of various essential factors such as maximum momentary water consumption, an average flowrate, the piping system from a water tank to the points of use, and some other points relating to the piping.

10. Ultraviolet Radiation (UV) Lamps for Disinfection

Although UV lamps may be placed in the running water pipes for disinfection against microorganisms grown, the bactericidal effectiveness of any UV lamps is so limited that

mastering of the principles in UV lamps should be premised on the application. Points to consider in proper design of UV lamp installation are indicated below:

(1) A UV lamp with a wavelength of 254nm is commonly used for disinfection, and hence careful attention should be paid to the limited bactericidal effect, which is exercised only within narrow emitted spectra close to the irradiated wavelength. Further, the disinfection efficacy will vary with water temperature, flow rate, the intensity and duration of irradiation, and the types of target microorganisms. It should also be noted that microorganisms cannot be completely eliminated by UV irradiation, as some UV irradiated microorganisms may assume such phenomena as photo-reactivation and/or dark-reactivation.

(2) When ~~If~~ UV lamps are placed in the ~~n~~ loop for the purpose of disinfection, the locations of the lamps should appropriately be selected in view of their inherent advantageous efficacy.

A2.2 Validation of Pharmaceutical Water

A validation program for pharmaceutical water equipment is to establish the water quality monitoring program and the operation and maintenance program for equipment control including the sampling plan as well as the qualification of equipment design, installation, operation and performance.

1. Determination of quality characteristics of pharmaceutical water to be validated
2. Determination of equipment appropriate for manufacturing water of intended quality from source water
3. Selection of equipment, process control, and a monitoring program
4. Design Qualification (DQ)
5. Installation qualification (IQ)

IQ of equipment should include the following:

(1) Calibration of instruments

(2) Qualification in that all pharmaceutical water equipment as shown in the specifications is installed on the~~ir~~ drawings, and ready for operation as well as verification of instruments.

6. Operational Qualification (OQ)

OQ of equipment should include the following:

(1) Qualification of the reliable operation performance of equipment, alert system, and control system

(2) Qualification of the appropriateness of established alert and action levels

7. Performance Qualification (PQ)

In the early stage (phase 1) of PQ, ~~it~~ the capacity of equipment enough for the stable manufacture and supply of pharmaceutical water in the required quality should be qualified.

In the subsequent stage (phase 2), alert and action levels for the required water quality should be established, and SOPs for routine control should also be established for the purpose of effecting this stage. However, at the start of this qualification, the capacity of equipment to produce water meeting predetermined specifications should be ascertained for at least 3 consecutive days to 1 week at all points of use in critical processes for the systems of WFI and purified water, and at points of use in the sub-loops and critical processes for the equipment applied to source water and feed water. The same ascertainment of the above items should be followed to conduct PQ at the Phase 2 over 1 year on documented procedures and control criteria to obtain the practical data of seasonal variations in water quality and to confirm secure water system performance. During this phase-2 period, the frequency of the replacement for parts and instruments concerned should be examined, and potential problems with routine control should be extracted to take effectual measures for solution.

In the final phase (phase 3), constant and stable pharmaceutical water production should be ensured in the required quality within the alarm level on the trend analyses of the data on treated water given under the influence of seasonal variations in the quality of source water, so as to make a full report on the results~~,~~ and to evaluate the reliability of the entire equipment control program.

8. Equipment maintenance program

The procedural or other related documents on the periodical review of the process control of validated equipment for pharmaceutical water should appropriately be drawn up to be actually conducted, and also the implementation plan with a schedule and procedures for the validation on periodical revalidation including recalibration should adequately be made into practice so that some preventive action or corrective action including proper change control should be taken into account of the results on occasional demand.

A2.3 Routine Control of Pharmaceutical Water

A2.3.1 Outline

The demonstrated process qualification fully implemented at the initial validation stage should be premised on the routine and periodic control programs of pharmaceutical water. The routine control should include conductivity and total organic carbon (TOC) essential as critical control parameters, and the periodic control should include these two parameters as well as additional control parameters such as the counts of viable microorganisms, endotoxins, and particulate matter, depending on the

intended use of the water. The frequency of measuring these parameters should be determined based on the stability of water quality. For more details on the ~~r~~ routine control of pharmaceutical water, refer to the “Quality Control of Water for Pharmaceutical Use” in the General Information ~~section~~ of the Japanese Pharmacopoeia 16.

A2.3.2 Sanitization

The water sanitization system should be validated to demonstrate the capability effective in reducing microbial contamination to such an acceptably low level as to be maintained. For the heat sanitization system a heat distribution test should be made to demonstrate that heat is distributed throughout the entire water system. The chemical sanitization system needs the demonstration that a selected chemical agent is spread throughout the entire system at an optimal bactericidal concentration. It is also required to demonstrate ~~y~~ that any residual chemical agent can effectively be removed after sanitization. In general, the frequency of sanitization should be determined based on monitoring results for the water equipment in order to adequately operate the equipment under microbiologically well-controlled conditions and to maintain the bacterial count below the alert level.

A2.3.3 Water Sampling

A monitoring program for pharmaceutical water equipment should be implemented at an appropriate frequency to ensure that the equipment is well managed and controlled and allows water of required quality to be continuously produced. Water should be sampled at the points that the representative water quality in the process or the distribution system can be expected to be shown, and the sampling frequency should be established based on validation data so that sampling locations should be determined to cover all critical regions in the system~~s~~. A sampling schedule should be laid out in view of required quality characteristics of water to be collected. For example, as equipment for WFI must meet microbiologically strict control requirements, the sampling frequency for WFI needs to be higher than that for other types of pharmaceutical water.

Any water sample for microbiological testing should be tested immediately after collected, or the sample should appropriately be stored for the following analysis. When the sample stored for a certain period, the records of ~~n~~ storage conditions and time should be kept.

Microbiological analysis of sampled running water only indicates that any presence or situation of microorganisms in the pharmaceutical water will be suspected or supposed. Therefore, airborne microbial counts are used as an indicator of contamination for the pharmaceutical water equipment and also serve as a basis for establishing the alert level for the equipment. If a high level of airborne microbial counts is consistently found, this phenomenon will indicate some growth on the biofilm so

that appropriate control measures should be used.

A2.3.4 Alarm Level and Action Level

A quality monitoring program should be developed and implemented to ensure that pharmaceutical water is constantly produced at acceptable quality, when pharmaceutical water equipment is continuously operated within the design specifications. Monitoring data obtained should be compared with established process parameter limits or product water specifications. In addition, appropriate alert and action levels should be separately established on referencing the "Quality Control of Water for Pharmaceutical Use" in the General Information of the Japanese Pharmacopoeia 16 and used for process control as well as in judging the adequacy of operation conditions of equipment.

A2.3.5 Microbiological Monitoring Program

The primary purpose of the microbiological monitoring program for controlling pharmaceutical water equipment is to predict deterioration of microbiological quality of water and to ensure water quality by maintaining constant function of the pharmaceutical water system to prevent undesirable effects of microbiological deterioration on product quality. The microbiological quality of generated water should be controlled at an appropriate level by not only counting but also identifying the type of microorganisms present in the water system with the trend analysis approach.

Although it is ~~not~~ unnecessary to detect all types of microorganisms present in water; a monitoring approach capable of detecting the widest possible range of microorganisms including any microorganisms of slow growth should be adopted. The microbiological limits for pharmaceutical water should be appropriately established by referencing the limits specified in "Microbial Limit Test" in the General Tests, Processes, and Apparatus section of the Japanese Pharmacopoeia 16. If the microbial count exceeds the specified action level during validation or routine control, microorganisms should be identified or have their properties examined. If specific microorganisms are detected in large quantities, possible biofilm formation in the water system should be suspected, and appropriate sterilization or sanitization should be implemented to decontaminate the system.

A2.3.6 Monitoring of Conductivity and Total Organic Carbon (TOC) in Pharmaceutical Water

The procedures of the action levels or alert levels for conductivity and TOC should conform to those shown in the Microbiological Limits.

When water quality is controlled based on conductivity and TOC, no tests of individual metals or

inorganic ions may be made. The tests of these metals and ions, however, should preferably be made to clear up the causes whereby these parameters exceed the action or alert level.

A2.4 Training of Personnel Engaged in Pharmaceutical Water Equipment

An appropriate education and training program should be prepared concerning the production and quality control of pharmaceutical water and be conducted periodically and as needed for personnel engaged in the operation, maintenance, and control of the facility and equipment as well as water quality control in order to produce and control pharmaceutical water in the required quality level. Education and training results should be recorded in writing and retained in an archive. Main education and training items included in the program are listed below. These items may be performed at one time or successively over scheduled courses.

1. Relationship between pharmaceutical water quality and pharmaceutical product groups classified by the types of water used
2. Relationship between variations in source water quality, pharmaceutical water equipment, and pharmaceutical water quality
3. Control methods for pharmaceutical water equipment (including methods for sanitization , sterilization, and disinfection)
4. Test methods and control limits for pharmaceutical water
5. Ecological activities of microorganisms present in pharmaceutical water equipment (e.g. inner surface condition of pipes, influence of water flow, formation of biofilms and endotoxins, etc.)
6. Sampling procedures and precautions for sampling
7. Validation, change control, and deviation control for pharmaceutical water equipment

A2.5 Maintenance and Control of Pharmaceutical Water Equipment

A preventative maintenance program should be established and implemented to maintain pharmaceutical water equipment under well-controlled conditions. The program should include, but not ~~be~~ limited to, the following items:

1. Procedures for operating water equipment
2. Programs for monitoring critical water quality characteristics and equipment-operating conditions
3. Schedules for periodic sanitization
4. Preventative maintenance and calibration of each component of water equipment
5. Change control of water equipment and operating conditions

6. Procedures for temporary stoppage and resumption of water equipment

   In particular, procedures for the stoppage and resumption of ultrafiltration membrane treatment equipment should be carefully evaluated by taking into account risk of leakage due to functional degradation of membrane surfaces

6. Understanding of water equipment and its maintenance

A2.6 Change Control

When water equipment is remodeled or expanded or system operation procedures are modified, potential impact of these changes on the quality of pharmaceutical water should be evaluated. If the reevaluation of the equipment is judged to be necessary, equipment properties concerned should be validated again, as appropriate. Procedures for change control should be established as part of an equipment maintenance program. These Change control procedures should also be established in the equipment maintenance program as part of validation and maintenance and included.

A2.7 Deviation Control

When parameters for the pharmaceutical water equipment may exceed the predetermined alert or action levels, procedures to be taken should be documented in advance. If any deviations from the action level occur, at least the following items should be recorded:

1. Procedures for resampling and retesting
2. Reporting procedures
3. Procedures for the action of pharmaceutical water and pharmaceutical products manufactured using pharmaceutical water
4. Preventive measures
5. Corrective measures
6. Reevaluation of the monitoring program and established alert and action levels

A3 Pest Control of Aseptic Manufacturing Facilities

A3.1 General Requirements

Pest control of facilities for manufacturing sterile pharmaceutical products (as well as pharmaceutical manufacturing facilities in general) is critical in maintaining a clean manufacturing environment. Identification of insect species found within aseptic processing areas is also critical for maintaining cleanliness of facilities, since arthropods serve as an indicator of the presence of mold-induced food chains and are indicative of potential problems in overall biological cleanliness. Arthropods have a rich bioburden of microorganisms and their spores on their bodies. Thus, proper

pest control is important from the view point of microbiological control of sterile pharmaceutical products.

Arthropods captured in pharmaceutical manufacturing facilities may include members of Insecta, Arachnida (spiders, mites), Chilopoda (centipedes), and Isopoda (sow bugs) classes. In this document, these arthropods are collectively referred to as “arthropods.”

Although quite rare, arthropods may be found in APAs. An appropriate sampling method for arthropods should be developed for estimating the population of minute arthropods in very low density. Separately, a suitable pest control program should be established and implemented to monitor and remove arthropods (especially fungivorous arthropods) found inside facilities, because arthropods are rarely carried into or invade APAs from the outside.

A3.2 Pest Control Program

1. Pest control programs applicable to each clean area should be established and implemented, and control practice records should be produced and retained.
2. Pest control programs should preferably include the following procedures:
   (1) Procedures to be taken from pest monitoring activities to the implementation of corrective actions
   (2) Pest control procedures that are to be implemented after pest monitoring results which deviate from established control criteria
   (3) Follow-up survey procedures for pest monitoring data which deviates from control criteria
   (4) Survey procedures for identifying the source of fungal contamination, if fungivorous arthropods are detected
   (5) Reevaluation of cleaning procedures if arthropods that feed on organic matter in dust are detected
3. Scope of pest monitoring

   Arthropods should primarily be monitored in indirect support areas in manufacturing facilities for sterile pharmaceutical products, and then, as monitoring results may require, in direct support areas to assess potential influence of arthropods on the quality of pharmaceutical products. The scope of pest monitoring should preferably be examined at each instance of newly constructing or remodeling facilities and equipment.
4. Sampling method and size
   (1) Equipment used for pest monitoring should be carried into the APA while exercising suitable precautions to avoid contamination of the production environment.

(2) Sampling methods should be established by taking into account the ecology of target arthropods that may inhabit manufacturing facilities.

5. Control standards

(1) Pest control acceptance criteria should be established.

(2) In a practical manner, pest control should be conducted based on the maximum number of arthropods, not the mean, as most arthropods are not uniformly distributed but congregate in clumps.

(3) Arthropods emerging inside processing/manufacturing areas should be counted separately from those invading from outside.

(4) Not only should the insect population be evaluated, but also the growth and distribution pattern.

(5) Insect monitoring results should be classified and evaluated by the area and type of arthropods.

6. Corrective and preventive actions

(1) Corrective and preventive actions should be promptly implemented based on monitoring results, and the effectiveness of these actions should be confirmed.

(2) Historical records regarding the growth and distribution patterns of arthropods should be analyzed, and appropriate preventive measures should be implemented based on results of trend analysis.

A3.3 Preventive Measures against Arthropods

Appropriate and effective species-specific pest control measures should be developed and implemented, targeting arthropods identified through the monitoring program.

1. Species-specific insect control

Different species of arthropods have different food habits, life history, ecology, and behaviors. The pest control program should be tailored for the treatment of individual target species. For example, an existing cleaning program should be reviewed to strengthen the control of arthropods that consume organic matter in dust, and a fungus treatment program should be implemented for fungivorous species.

2. Fungus control

In most cases, the appearance of arthropods in clean areas may be associated with fungi growing in a facility with inadequate design and operational features. If fungivorous arthropods are detected, the design, construction and operation of the facility should be reevaluated, and fungus control measures should be implemented or reinforced.

3. Supervision of facility and its design for the prevention against insects

   If there are signs or evidences of insect invasion from outside or if abnormal insect population growth is observed inside the facility, if there are insects invading from outside or the population of insects breeding inside, facility and its design should be reevaluated to prevent the insects.

4. Precautions in the use of insecticides

   (1) Insecticides should not be used in clean areas, as a general rule.

   (2) When the use of insecticides is necessary to control abnormal population growth of insect pests, appropriate preventive measures should be instituted to prevent the contamination of pharmaceutical products. When insecticides are used in controlled but unclassified areas, due care should be exercised to prevent the insecticides from dispersing into the surrounding areas.

   (3) When insecticides are used in clean environments, the surfaces of these areas should be cleaned following application using suitable method to remove the insecticides. Following cleaning all surfaces should be confirmed to be free from insecticide residues.

   (4) For all insecticides used in pharmaceutical manufacturing facilities, the Material Safety Data Sheets (MSDS) and use records of the insecticides should be retained for archival purposes.

A4 Biosafety and Biosecurity Measures

Biotechnological processing using microorganisms and toxins for manufacturing pharmaceutical products must be managed by physical containment facilities, equipment, and/or procedures in addition to the procedures for sterility assurance (Guidance on Biosafety Practices in Manufacturing Facilities for Biopharmaceutical Products, Notification No. 14 of the Inspection and Guidance Division, PMSB dated February 14, 2000, and Laboratory Biosafety Manual Version 3 issued by WHO).

Biological and pharmaceutical products manufactured using genetic engineering technologies should be manufactured in compliance with the Guidance on Regulations for the Transport of Infectious Substances 2009-2010 issued by WHO, and biohazardous raw materials that require biosecurity measurements should be in compliance with the Act on Prevention of Infectious Diseases and Medical Care for Patients Suffering Infectious Diseases and Biorisk Management: Laboratory Biosecurity Guidance issued by WHO.

A4.1 Biosafety Levels

The manufacture of pharmaceutical products using microorganisms (the term "microorganisms" denotes both "viruses" and "bacteria" in this chapter) should be conducted at biosafety levels (BSLs) suitable for safe handling of materials depending on the level of risks from individual pathogenic microorganisms. Microorganisms used in the manufacture are classified into the three risk groups defined below, and BSL for manufacturing facilities are designated as BSL 1 to 3 consisting of the combined elements of physical capability of microorganism containment, availability of safety instruments and protective products against infection, and operational procedures to be implemented. As an exception, the procedures for inactivation or removal of microorganisms may be conducted in the manner typically applied to non-biological products.

1. Risk group 1 (BSL: 1): No known or minimal risk of exposure to pathogenic agents (e.g. pathogenic isolates of viruses for vaccine production, such as measles, rubella, mumps, chickenpox, BCG, etc.) for operators engaged in microorganism handling or in the surrounding area
2. Risk group 2 (BSL: 2): Moderate risk of exposure to pathogenic agents (e.g. *Bordetella pertussis*, *Corynebacterium diphtheriae*, *Clostridium tetani*, *Vibrio cholerae*, etc.) for operators engaged in microorganism handling and low risk for other operators in the surrounding area
3. Risk group 3 (BSL: 3): High risk of exposure to pathogenic agents for operators engaged in microorganism handling and low risk for other operators in the surrounding area. Person-to-person transmission of infectious diseases does not occur under routine working conditions. Effective therapeutic and preventive measures are available.

A4.2 Biosecurity Measures

Microorganisms and certain types of bacterial toxins have a great potential to damage regional societies surrounding laboratory facilities when dispersed or intentionally released. Therefore, biological security measures are usually required in biopharmaceutical sectors. Stringent control measures should be implemented and followed at the very least for registration or designation of operators engaged in operations, entry and exit from facilities, and storage and transfer of biomaterials, as described below:

1. Registration or designation of operators engaged in handling of microorganisms and bacterial toxins
2. Preparation of SOPs for storage, transfer, and transport of microorganisms and bacterial toxins and record keeping of storage, transfer, and transport practices

   In addition, microorganisms and toxins designated as specific pathogens by the Act on

Prevention of Infectious Diseases and Medical Care for Patients Suffering Infectious Diseases should be classified as Types 2, 3, or 4, in accordance with the Act, and facility construction, import, transfer, transportation, use, storage, and sterilization of such materials should be handled in compliance with governing laws and regulations.

A4.3 Biosafety Management Areas (Controlled Areas)

Biosafety management areas ("controlled areas") should be established which meet the levels of containment required for proper handling of microorganisms based on pathogenic potential of microorganisms to be handled. If the BSL of the controlled area is 2 or higher, international biohazard symbol containing the supervisor's name and emergency contact information should be displayed on entry and exit doors of the area.

The entry of non-registered personnel into controlled areas should be restricted by instituting appropriate measures or systems at the entrances/exits and in storage rooms of microorganisms and toxins, and entry and exit records of registered personnel should be retained as required by applicable regulations and guidelines established for handling microorganisms and toxins.

A4.4 General Requirements for BSL1

1. There are no specific biosafety requirements necessary for BSL1 for facilities and equipment.
2. Waste materials carrying risk of infection (the term "waste materials" includes carcasses and denotes materials contaminated with microorganisms in this document) should be sterilized with chemical agents or disinfected with heat and transferred out of the controlled area. The materials may be placed in leakproof containers and, after disinfection of their surfaces, transferred out of the controlled area. Then, the materials should be incinerated. It is acceptable to contract out the incineration, provided the materials are sterilized beforehand.

A4.5 General Requirements for BSL2

1. Any operations that may generate aerosolized microorganisms should be conducted using closed-system equipment provided with HEPA filters, safety cabinets (Class IIA or higher), or other equipment having a similar capacity for microorganism containment. In addition, air exhausted from such equipment or systems should be cleaned so as to completely eliminate aerosolized microorganisms.
2. Waste materials carrying risk of infection should be disposed of using one of the procedures below. The incineration of the sterilized materials may be contracted out.
   (1) Chemically disinfect or heat-sterilize waste materials, transfer them out of the controlled area, and burn them using an incinerator within the facility.
   (2) Place waste materials in leakproof containers to prevent dispersion during transportation, and after disinfection of their surfaces, transfer them out of the controlled area for incineration within the facility.
   (3) Transfer waste materials from the controlled area directly to either an incinerator or

sterilizer using an appropriately managed closed-system procedure, and then incinerate the materials within the facility.

3. Waste fluids containing microorganisms and fluids that come into direct contact with microorganisms should be disposed of after appropriate treatment with chemical disinfection or heat sterilization in a tank or other closed system placed inside or outside the controlled area.
4. The disposal of toxins and other wastes should be conducted while taking their properties into account.

A4.6 General Requirements for BSL3

1. Controlled areas designated for handling microorganisms that require BSL3 containment should be structurally separated from other areas.
2. Personnel entry into BSL3 facility should be controlled by displaying “restriction notices” and establishing procedures required to obtain permission to enter. Additionally, physical entry restrictions, such as a security door, should be installed.
3. Ceilings, walls, and floors of controlled areas should be smooth-surfaced, crack-free, non-dust- or debris-shedding, and resistant to chemicals or other types of disinfectants in order to maintain a closed system in these areas.
4. If air current is controlled in working areas of a controlled area, inward current should be secured to minimize leakage of microorganisms from the area. The direction of the current should be monitored by, for example, measuring and recording pressure differences against adjacent areas. Entrances to areas with pressure difference should be equipped with airlocks, and substantial pressure differences should be maintained in order to prevent inversion of pressure differences or air currents with the surroundings.
5. Effective disinfecting apparatuses or devices should be available in BSL3 areas to implement appropriate disinfection measures against pathogenic contamination.
6. Faucets in restrooms, washing sinks, and other places should be touchless, elbow-handled, or pedal operated to prevent cross-contamination.
7. Work areas in the controlled area should be sufficiently spacious to prevent contamination during operations.
8. The HVAC system (e.g. ducts) should be structurally designed to facilitate sterilization with gases, as appropriate.
9. Any operation which may carry a risk of generating aerosolized microorganisms should be conducted in a safety cabinet (Class II or III) equipped with HEPA filters or other closed and

contained systems of an equivalent or higher safety level. Additionally, air from such a work environment should be evacuated outside the facility after passing through HEPA filters.

10. Air in controlled areas should be filtered and evacuated through an independent HVAC system equipped with HEPA filters.
11. BSL3 facilities should be designed to be capable of physically containing microorganisms within the controlled area under any contingent circumstances, such as shut-down of the HVAC system.
12. An emergency power supply should be available to maintain continuous operation of the HVAC system in the event of power failure.
13. The drain system should be mounted with devices to prevent backflow.
14. Waste fluids containing microorganisms or those that come into direct contact with microorganisms should be chemically disinfected or heat sterilized in a tank or other closed system in either controlled or non-controlled areas and then disposed of.
15. Waste materials carrying risk of infection should be disposed of using one of the following procedures:
    (1) Chemically disinfect or heat sterilize waste materials, transfer them out of the controlled area, and burn them using an incinerator within the facility.
    (2) Place waste materials in leakproof containers to prevent dispersion during transportation, and after disinfection of their surfaces, transfer them out of the controlled area for incineration within the facility.
    (3) Transfer waste materials from the controlled area directly to either an incinerator or sterilizer using an appropriately-managed closed-system procedure, and then incinerate the materials within the facility.
16. Personnel should use infection protection supplies (e.g. clothes, mask, gloves). Gowning and degowning procedures should be appropriate. Infection protection-reinforced clothes such as positive-pressure protective suit should be used if the situation requires it.

A4.7 Emergency Procedures

A4.7.1 Emergency Safety Measures

The following emergency procedures should be established and documented in preparation for emergency situations such as leakage of aerosolized microorganisms or culture media, exposure to microorganisms, fire outbreak, or natural disaster:

1. Rescue of personnel exposed to microorganisms, emergency attention and first aid for injured personnel, and therapy for personnel infected with microorganisms

2. Wastes material containment methods
3. Procedures for decontamination
4. Emergency SOPs and communication networks

A4.7.2 Preventive and Counter Measures for Accidents Due to Specific Pathogens

The term “accident” in this document means a loss, theft, disappearance, intentional release, etc. of retained specific pathogens and other microorganisms. The following procedures should be established and documented in preparation for accidents:

1. Establishment of measures to both prevent and respond to accidents
2. Emergency communication networks
3. Reporting and notification procedures for accidents (as required depending on accident classification)

A4.8 Personnel Training

Personnel who engage in operations in controlled areas should undergo biosafety and biosecurity training programs prior to initial engagement and at periodic intervals thereafter. The education and training programs should cover the following:

1. Characteristics of microorganisms to be handled in the controlled area (e.g. BSL, mode of infection)
2. Procedures for entering and exiting the controlled area
3. Procedures for handling and operating equipment and devices installed in the controlled area
4. Procedures for safely handling microorganisms
5. Records of microorganism retention and supply
6. Containers and procedures for transporting infectious substances
7. Procedures for disposal of infectious waste materials
8. Emergency safety measures
9. Procedures for the use, storage, control, transportation, and disposal of microorganisms and for reporting/notification in facilities where specific pathogens are handled

A5 Chemical Hazard Control

A5.1 Principles

Control procedures for hazardous materials should be evaluated and established based on the assessment of potential health risks to patients—i.e. cross-contamination risks— as well as potential

health risks to factory personnel. The ICH Q9 guideline “Quality Risk Management” states: “Risk is defined as the combination of the probability of occurrence of harm and the severity of that harm.” Health risks for patients and factory personnel may be defined as the combination of the probability of contact with or extent of exposure to chemical substances (or drug substances) and a substance’s potential (or hazard) to cause health damage. Chemical hazard control should be planned and control measures implemented in accordance with the risk management process (Figure 1) proposed by the ICH Q9 guideline “Quality Risk Management.” It is important to develop and implement efficient measures to reduce the risks to permissible levels at every step of production process and throughout the lifecycle of a product.

Under no circumstances should hazard prevention be used to justify compromising or obfuscating the sterility assurance level of products.

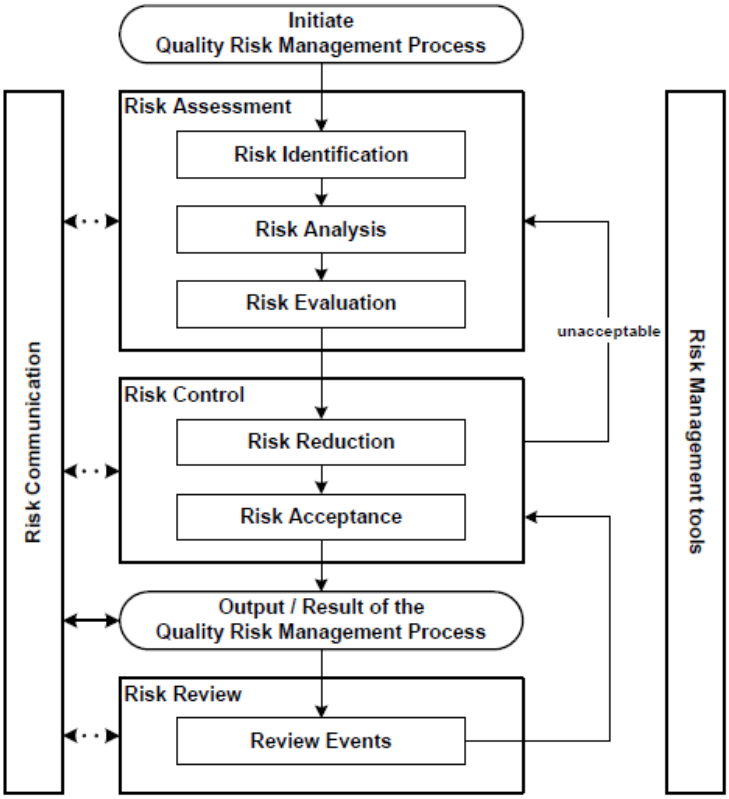

Figure 1. Overview of a Typical Quality Risk Management Process

A5.2 Risk Management Processes

A5.2.1 Identification of Risks (Hazards)

It is important to establish permissible exposure limits of individual chemical substances (or drug substances) based on scientific rationale, thereby potentially eliminating health hazards to patients and factory personnel. These limits are obtained by extrapolating data from animals (preclinical) or humans (clinical) to manufacturing plant setting. Such limits are defined as "permitted daily exposure (PDE)," "acceptable daily exposure (ADE)", or "acceptable daily intake (ADI)" in various guidelines.

The exposure limits thus established are based on the risk of damage to human health and are then used as reasonable references for determining safe exposure limits for work environments (e.g. acceptable exposure concentrations and residual amounts), permissible cross-contamination limits, and permissible residue levels on product contact surfaces. These limits provide the basis for establishing manufacturing conditions adequate for ensuring that health risk to patients and factory personnel are consistently below the maximum acceptable exposure level.

A5.2.2 Risk Analysis (Exposure Analysis)

The risk level for patients and factory personnel exposed to chemical substances depends on the nature or properties of chemical substances (e.g. powder, liquids, or aerosol form; particle size; specific gravity; solubility; etc.) over the production system life-cycle (all manufacturing steps, including production, changeover cleaning, and parts replacement) in each manufacturing process as well as the properties of the manufacturing processes themselves (e.g. open/closed systems, containment equipment, protectors, dust collection, clean-in-place systems, wet-in-place, etc.). Exposure analysis should be performed at both the steady- and non-steady-state production system's life-cycle, examining potential risk modalities such as the loss of containment equipment integrity.

A5.2.3 Risk Assessment

Outcomes of risk analysis regarding human exposure to hazards should be evaluated in comparison with established exposure limits to assess potential health risks to patients and factory personnel. Potential health risks to patients are only acceptable if the cross-contamination of one pharmaceutical product with another product is known not to exceed defined cross-contamination limits during the manufacturing process of a pharmaceutical product. However, health risks to factory personnel may be acceptable if exposure to chemical substances is known to be controlled to quantities equal to or less than the ADE via exposure routes such as inhalation, direct contact, and oral.

A5.2.4 Risk Control

If risk assessment results are judged to be unacceptable, appropriate risk mitigation measures should be implemented in line commensurate with the magnitude of the risks. While risk control measures vary, they should always address the following issue according to the prioritized list shown below:

- Removal of target chemical substances
- Use of alternative chemical substances
- Use of containment equipment (as a physical risk mitigation measure)
- Protection of personnel working in an open system

The basis of risk control is to prevent dispersion of highly active (hazardous) chemical substances into areas where residue control is not feasible or where decontamination is difficult.

The construction of a dedicated facility or the use of dedicated equipment should be considered in the course of developing control measures if validation-based cleaning procedures cannot be securely established or if risks of transferring chemical substances to non-product contact areas or risks of contaminating products with dispersed chemical powder are not acceptable.

A5.2.5 Risk Review

Once chemical hazard preventive measures have been implemented based on a systematic risk assessment and the implementation of well-defined control activities, the, results of the risk management activities should be reviewed to confirm that the expected outcome has been achieved.

Measuring amounts of chemical dispersed and chemical residuerecovered from equipment surface is a valuable and effective means of risk review.

A5.2.5 Risk Communication

Risk management processes included in the chemical hazard control program should be systemically implemented by an organization with well-defined decision-making authority and responsibility. The implementation should preferably be undertaken by interdisciplinary teams comprised experts, as recommended in the ICH Q9 guideline. When teams are formed, they should include experts from appropriate functional disciplines (e.g. quality unit, business development, engineering, regulatory affairs, production operations, sales and marketing, legal, statistics, and clinical), in addition to individuals knowledgeable on the quality risk management process.

A5.3 Personnel Training

1. The education and training programs for personnel engaged in chemical hazard control should cover the following:
   (1) Properties of chemical or drug substances to be handled
   (2) Procedures for entering and exiting the controlled area
   (3) Procedures for handling and operating equipment and devices within the controlled area
   (4) Procedures for disposal of active waste materials
   (5) Emergency safety measures
2. Education and training programs for personnel engaged in emergency operations should include the following topics:
   (1) Emergency treatment and first-aid care for factory personnel
   (2) Decontamination procedures
   (3) Emergency communication networks

A6 Tests and Inspections

A6.1 Endotoxins

A6.1.1 General Requirements

1. The possibility of endotoxin contamination should be considered and appropriate preventive measures implemented for raw materials, containers, closures, pharmaceutical water used to manufacture parenteral pharmaceutical products, and surfaces of manufacturing equipment contacting products.
2. Surfaces of manufacturing equipment contacting products should be properly cleaned, dried, and maintained in a clean condition to prevent an increase in bioburden and associated endotoxin levels.
3. The final rinse of surfaces of manufacturing equipment contacting products as well as containers and closures should use water for injection to prevent contamination with endotoxins. The manufacturing equipment after washing should be kept dry unless immediately followed by sterilization.
4. The efficiency of endotoxin removal from containers and closures should be validated when the removal is performed by heat inactivation, surface washing, or adsorption or membrane filtration of prepared drug solution.
5. Endotoxin testing procedures should generally comply with the Endotoxins Test in the Japanese Pharmacopoeia. Prior to testing, a test for interfering factors should be performed to

identify the maximum valid dilution to confirm the absence of enhancing or inhibiting factors for the reaction in sample solutions.

A6.1.2 Validation

1. When endotoxin inactivation or removal is performed by heating, washing, membrane filtration, or adsorption, the post-processing residual endotoxin level should be verified to fall within specified control limits by determining the post-processing removal rate after loading a known amount of endotoxin.
2. Endotoxin testing should be supplemented by appropriate method validation.
3. Lysate and other reagents necessary for the endotoxin test should be appropriately controlled with regard to storage temperature and expiration date.

A6.2 Insoluble Particulate Matter

A6.2.1 General Requirements

1. The amount of insoluble particulate matter remaining on washed containers, closures, and drug solution-contact surfaces of manufacturing equipment after filtration sterilization as well as in filtered drug solution should be controlled within certain acceptance limits.
2. Insoluble particulate matter occurring with time after production by interaction between containers or closures and drug solution or by aggregation of high-molecular-weight substances such as proteins should be closely monitored to control the levels below maximum acceptable limits. The control efficiency should be verified by long-term stability tests.
3. Insoluble particulate matter testing procedures should generally comply with the Insoluble Particulate Matter Test in the Japanese Pharmacopoeia.

A6.2.2 Validation

The Insoluble Particulate Matter Test should be supplemented by appropriate method validation.

A6.3 Container Integrity

A6.3.1 General Requirements

1. Containers for sterile pharmaceutical products should be closed by an appropriately validated method. The integrity-related parameters should be adequately controlled, since the integrity of the container-closure system may be compromised, if operation conditions of

manufacturing equipment are not optimal.

2. Flawed containers or closures may become a contributory factor to the compromise of the integrity. The integrity should be ensured by routine monitoring or by 100 percent inspection of containers or closures, and necessary safety measures be implemented to prevent the supply of pharmaceutical products with a risk of non-sterility.
3. Containers closed by fusion such as glass or plastic ampoules should be subjected to 100 percent integrity testing. Samples of other containers should be checked for integrity sccording to appropriate procedures.
4. Container integrity and hence product sterility should be verified to be maintained until use.
5. Procedures for the integrity test should be established in a manner suitable for properties of individual containers and closures.

A6.3.2 Validation

1. The container integrity test to be employed should be validated by appropriate methods.
2. The container integrity test should take at least the following test conditions into consideration, wherever feasible: temperature variations during product storage, packaging forms, vibrations and shocks during transportation, variations in atmospheric pressure during air transportation. Rationale for these conditions should be documented.

A6.4 Visual Inspection

A6.4.1 General Requirements

1. If the sterility of pharmaceutical products is ensured by eliminating products that exhibit observable container integrity failure, the relationship between container integrity and visual characteristics should be appropriately defined for use as visual inspection criteria.
2. The visual inspection criteria should be optimized for each formulation of each pharmaceutical product based on product characteristics.
3. Standards of foreign matter in pharmaceutical products should be established based on the Foreign Insoluble Matter Test for Injectables in the Japanese Pharmacopoeia. Standards for “readily detectable foreign insoluble matter” and “clearly detectable foreign insoluble matter” should be specified for features of pharmaceutical products and types of foreign matter.
4. Pharmaceutical products should be subjected to the inspection of all products (“100% inspection”) during the manufacturing process to remove products containing “readily detectable foreign insoluble matter” or “clearly detectable foreign insoluble matter.” This 100% inspection should be followed by sampling inspection, as appropriate. The sample size

for sampling inspection should be sufficient for statistical analysis with respect to batch size (refer to AOL sampling plan, as an example).

5. The test method of visual inspection should be specified in SOPs. For example, visual inspection by humans should include, but not be limited to, the following test conditions:

   (1) Inspection procedures, inspection pitch, time required for inspection per unit of inspection, and intervals of inspectors' rest breaks

   (2) Inspection benches, inspection conveyers, inspection lamps, inspection magnifiers, and inspection posture (e.g. seated on chair)

   (3) Light intensity ininspectionposition, light intensity in inspection area or room, and color of background plate

   If all pharmaceutical products are required or planned to be visually inspected during the manufacturing process, the conditions for inspection such as the duration of observation and light intensity, should be specified and optimized for individual products to completely remove "readily detectable foreign insoluble matter" and "clearly detectable foreign insoluble matter." The light intensity over the area of inspection should range from 2000 to 3750 lux if sampling inspection or quality test is performed after 100 percent visual inspection. The time required for visual inspection should be 5 seconds per unit of inspection per background color of white and black each. The light intensity and duration of observation may be increased, as appropriate.

6. If visual inspection is conducted using automatic inspection equipment, at least the following matters should be determined and specified:

   (1) Model of automatic inspection equipment, speed of work, and time required for inspection per unit of inspection

   (2) Assessment methods for the performance of the equipment at the beginning and end of inspection operation as well as periodic verification of the performance using reference standards

   (3) Calibration

7. When a boundary sample is to be prepared for use in the interpretation of inspection results, the quality of the sample should be evaluated and approved by the quality control department. Since boundary samples deteriorate or decompose over time, an expiration date should be set or sample quality should be periodically evaluated.

A6.4.2 Validation

1. When visual inspection is conducted manually by the inspector, the ability of individual

inspectors should be evaluated using boundary samples to ensure that they have the predetermined competency and satisfy qualification requirements on visual inspection. Their ability as well as eyesight should be assessed periodically.

2. The capacity of automatic inspection equipment should be periodically validated using boundary samples to ensure that the equipment has the required capacity for inspecting and eliminating foreign insoluble matter.

3. Samples of foreign insoluble matter to be used to validate the inspection process should preferably be obtained through actual production. The use of validation samples should be approved by the quality control department.

B Revision Records

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