(G) Operators' name

3) Any materials that have not been successfully sterilized, as judged in accordance with the criteria, should be handled as stated in relevant documented procedures. Causes of poor performance should be investigated and appropriate corrective actions implemented.

4) Storage conditions for sterilized materials and products should be suitable for preserving and maintaining their specifications, sterility, and dryness. Location, methods, environmental conditions, and duration of storage should be predetermined and sterilized materials and products should be managed accordingly.

14.3. Dry Heat Sterilization

The basic requirements and control procedures for dry heat sterilization should be consistent with those mentioned for autoclaving, above. Additionally, the following criteria specific to dry-heat sterilization should also be met.

1) When depyrogenation is required for dry-heat sterilization, the efficacy of the process should be validated by appropriate means, such as the use of an endotoxin challenge test.

2) The endotoxin content of materials to be sterilized should be periodically measured prior to sterilization.

3) HEPA filters mounted on sterilizers should be periodically tested for leaks to check the capacity of the filters. Ideally, the leak test should be performed once every 6 months; however, it must be performed at least once a year.

4) Whenever a continuous sterilizer is used, airflow should be monitored to ensure that it does not flow from a non-sterile to a sterile area during operation.

14.4. Electron Beam and Gamma Ray Sterilization

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

1) The dose of radiation necessary to achieve sterilization should be based on acceptable validation data obtained using actual or dummy material to be sterilized.

2) The sterilization process parameters should be established based on validation data. Adequate records are also required to document that the irradiation has been performed and the parameters attained.

3) The bioburden of materials to be sterilized should be determined prior to sterilization at a predetermined frequency.

4) The loading configuration of materials to be irradiated determined by validation testing should be documented. Procedures to be employed for the adequate storage and control of materials before and after sterilization should be also documented.

5) The name, loading configuration, quantity, date of irradiation, and dose absorbed should be documented for all irradiated materials. These irradiated materials should be identified appropriately (e.g., sterilization batch numbers) so as to enable the traceability of individual materials.

6) The word "irradiated" should appear on each of the smallest packaging units of all irradiated materials to ensure proper storage and control.

7) The radiation dosage measurement system used should show traceability with national standards.

8) When irradiation sterilization is contracted out, the contractor and the contractee should address the items listed below (at the minimum) in writing:
   (A) Preservation of the sterility of contracted goods during transportation
   (B) Layout of the certificate to be issued by the contractor indicating that the contracted goods are irradiated
   (C) A statement of the conditions under which each lot of irradiated materials was sterilized (the contractee will provide this document to the contractor upon request)
9) The radiation dosage should be checked at an appropriate frequency to ensure its effectiveness for repeated irradiation sterilization cycles.

14.5. Microwave Sterilization

The basic requirements and control procedures for microwave sterilization should be consistent with those mentioned for autoclaving, above. Additionally, the following items specific to microwave sterilization should be controlled.

1) Prior to sterilization, a permit to use microwave sterilization in a given building or facility should be applied for and granted, as stated by the Radio Law.
2) Generally, microwave sterilization should be performed at a frequency of 2450 ± 50 MHz.
3) Microwave sterilization should be applied only to liquid or high-water-content materials placed in tightly sealed containers.
4) Containers must be able to withstand increased inner pressure during the sterilization process.
5) The conditions of sterilization should be established based on applicable validation data for each type of material to be sterilized.
6) When microwave sterilization is employed for the terminal sterilization of drug products, sterilization success should be confirmed by monitoring and recording the sterilization temperature of each product container.
7) It should be confirmed that the sterilizers are functioning properly by monitoring the microwave signal.
8) It should be confirmed that any signal leakage falls within specified limits.
9) The magnetron used to generate high-frequency radio waves should be monitored to control its use. Each use of the magnetron should be recorded, and the data obtained should be incorporated into the maintenance program for the device.

15. Clean-In-Place (CIP) Systems

A clean-in-place (CIP) system is a method designed to clean an entire system of equipment with appropriate cleaning agents *in situ* without disassembling any components, including pipes.

15.1. Design Consideration for CIP Systems

When designing the equipment, apparatuses, and pipes to be subjected to CIP, and the cleaning agent supply system for a CIP, the items listed below should be taken into consideration:

1) The inner surfaces of the equipment, systems, and pipes that are to be subjected to CIP should be smooth and should be selected and designed to facilitate effective cleaning. The structure

of these pieces of equipment, systems, and pipes should be suitable for inspection and verification of cleaning results.

2) "Dead legs" in pipes connected to equipment and systems should be minimized.
3) Cleaning agent supply systems for CIP should be designed to maintain a stable flow rate, pressure, temperature, and concentration of the agents.
4) Critical parameters such as flow rate, pressure, temperature, and concentration of cleaning agents should be monitored and recorded using appropriate devices built into the CIP system.

15.2. Selection of Cleaning Agents

1) Cleaning agents should be selected based on ability to eliminate residues, physical and chemical characteristics of residues to be removed, and compatibility with manufacturing equipment.
2) There are various types of cleaning agents available, for example water, hot water, detergents, alkaline solutions, hot alkaline solutions, organic solvents, etc. All cleaning agents, their residues, and their components need to be reduced to below specified limits with final rinsing.
3) The quality of water used for the final rinse of surfaces that may come into direct contact with the drug product should be of the same quality as the water used for product formulation.
4) The cleaning agent quality specifications should be established and documented.

15.3. CIP Process Parameters

Of the surfaces to be cleaned by the CIP system, those that are difficult to clean should be identified at the validation stage, and, when necessary, supplemental operations or processes should be established to achieve the predetermined level of cleanliness. The CIP critical process parameters for the control of the cleaning process should be specified and documented based on validation data and must result in predetermined levels of cleanliness. Such parameters should take the following into consideration:

1) Type and concentrations of cleaning agent
2) Flow rate of cleaning agent
3) Duration of contact between the surface and cleaning agent
4) Temperature and pressure of cleaning agent
5) Total cleaning time
6) Parameters that indicate acceptable cleaning agent residue levels, such as conductivity, pH, and total organic carbon (TOC) (to be determined by referring to the composition of the cleaning agents)
7) The maximum allowable time that may elapse between completion of processing and start of CIP.

15.4. Routine Monitoring and Control

The process parameters and control items for routine CIP monitoring and control should be identified and documented based on validation data. Data on each CIP operation should be recorded and retained for each CIP process and reviewed periodically. CIP process records or other related records should include, but not be limited to, the following:

1) Date and time

2) Name of the system
3) Name and production batch numbers of drug products manufactured prior to CIP adoption
4) Name and production batch numbers of drug products manufactured after CIP adoption
5) Name of operators
6) CIP operating conditions
7) Verification of suitability for the CIP conditions employed
8) The allowable time between the completion of the CIP and the use of the CIP system
9) Establishment of an easy and clear system for distinguishing between the status before and after cleaning of the CIP operation
10) Verification of the calibration of instruments used to detect the completion of the cleaning process

16. Sterilization-In-Place (SIP) Systems

A sterilization-in-place (SIP) system is a method designed to sterilize an entire chain of equipment with appropriate sterilizers *in situ* without disassembling any components. In general, saturated steam is the most widely used sterilizing agent.

16.1. General Requirements

1) If a facility or equipment (e.g., tanks, filling lines, transfer lines, filtration systems, or water for injection system) cannot to be sterilized using an autoclave because of its size and/or shape, and is subjected to a Sterilization-In-Place (SIP) System, the sterilization efficacy of the SIP process [typically, a sterility assurance level (SAL) of $\leq 10^{-6}$] should be demonstrated using an appropriate parameter-measuring instrument such as temperature gauges, pressure gauges, thermocouples, and moist heat-resistant BI.
2) Steam to be used for SIP processes should be generated from purified water or water of not less than purified quality. The steam condensate should meet the specifications of water used for product formulation.
3) Locations that are particularly difficult to sterilize, so-called "cold spots," should be identified and the SAL achieved should be reviewed periodically.
4) The integrity of the sterilized system should be maintained after completion of the SIP process. Sterile gas (air or nitrogen) is usually drawn into the SIP system to purge steam and condensate from the system while the entire sterilized system is maintained under positive steam pressure until the system becomes ready for use. When a certain system is used under negative pressure or atmospheric conditions, the SIP system should be qualified to affirm that the conditions do not compromise the sterility of the entire system. The maximum allowable time between the completion of the SIP operation and use of the equipment system should be specified.
5) When SIP is not automatic, a procedure for manual operation should be established and strictly adhered to. Records of manual SIP operation, when performed, should be maintained as an evidence that the operation was conducted according to procedure.

16.2. Key Design Consideration for SIP Systems

The equipment to be sterilized by the SIP system should be compatible with the steam to be used and drug products to be sterilized. It should also be designed to not retain air or condensed water. The equipment design should take the following into consideration.

1) Equipment must have smooth inner surfaces.
2) Flow of steam must reach all surfaces to be sterilized.
3) Location of saturated steam introduction is appropriate and steam distribution is efficient.
4) Elimination of unnecessary branches of trapped air and condensed water, removal of unnecessary pipe branches, and minimization of dead legs
5) Appropriate slope of pipes
6) Appropriate location of steam and condensed water exhausts
7) Heat and pressure resistance of equipment
8) Compatibility between materials of construction and the quality of steam
9) Other appropriate measures in place to maintain the sterility of sterilized materials during and after SIP; for example, the installation of appropriate vent filters and maintenance of positive pressure

16.3. Personnel Training

Training for personnel engaged in SIP operations should include the following:

1) Structure of the SIP system and an overview of the process
2) Actions to be taken if an emergency involving the SIP process occurs
3) Other requirements, as applicable

16.4. Routine Monitoring and Control

1) Data should be recorded and retained for each SIP process and periodically reviewed. Each time the SIP operation is performed, it is recommended that the following parameters be continuously monitored and recorded via devices integrated throughout the entire system: temperature (e.g., temperature at the steam inlet, inside of the tanks, drain port), pressure (e.g., steam inlet, inside of the tanks, inside of the pipes), and duration of SIP processing. If continuous measurement and recording are not feasible, alternate measures should be instituted to confirm that the sterilization process parameter requirements have been met.
2) Process operation records and other records of SIP operation should include, but are not limited to, the following:
   (A) Date and time of operation
   (B) Name of the system
   (C) Name of operators
   (D) Operation conditions employed
   (E) Verification of suitability for SIP operation conditions
3) Establishment of an easy and clear system for distinguishing between the status before and after the SIP.

4) The integrity of sterile filters through which sterile gas is drawn and the vent filters on tanks and chambers should be checked periodically to verify that they are functioning properly. Critical instruments such as temperature gauges should be calibrated periodically.

17. Filling Process

17.1. Liquid Products

1) Documented procedures for the sterile filling of liquid drug preparations, from the process of solution preparation and sterilization to cleaning and washing after filling, shoud be established. Assignment of responsibility should be also included in the procedures.
2) When sterile products or sterilized containers/closures will be exposed to the environment during operations (such as for filling, stoppering, and freeze-drying) such operations should be conducted in a critical area (Grade A). Cap sealing should be conducted in a Grade C or higher area. Additional protective measures should be taken as appropriate, depending on the degree of contamination risks. The time period between stoppering and sealing should be as short as possible.
3) The manufacturing environment should be monitored throughout the sterile filling process, including during preparation. Monitoring data should be duly evaluated. It is recommended that particulate matter in critical areas (Grade A) be continuously monitored.
4) Equipment surfaces that come into direct or indirect contact with sterile drug products should be sterilized according to a validated sterilization procedure.
5) Sterilized equipment and utensils should be handled and stored in a validated manner that preserves their sterility until use.
6) Sterile bulk material should be prepared for use by placing them in sealed sterile containers equipped with gas-sterilizing filters, unless the material is to be subsequently filtered by a liquid-sterilizing filter. The integrity of all filters used for filtration should be verified both before and after use.
7) Connections between containers of sterile bulk material and sterile filling equipment should be made aseptically and should be performed only in critical areas (Grade A). It is acceptable to make downstream connections in Grade B or lower cleanliness environments if, after connection, they are sterilized using a SIP system. If bulk materials are filter-sterilized during the filling process following preparation, it is necessary to maintain sterility downstream from the filter.
8) Limits should be established for the time required to prepare sterile bulk material as well as the time between preparation for and completion of the filling process. The shelf-life of each prepared sterile bulk material should be specified. If bulk materials are prepared in a non-sterile state and sterilized subsequently by filtration during the filling process, the sterilizing filtration should take place as soon as possible after preparation to minimize the growth of microorganisms during storage.
9) Documented procedures for confirming the tightness of the seal on containers used in the preparation of sterile bulk materials as well as connectors on containers and filling equipment should be established. A schedule for gasket replacement should be also established.
10) The use of belt conveyors for transporting materials between APAs and adjacent areas of lower cleanliness levels is not recommended. When the belt conveyors need to be moved to an APA from an area of lower cleanliness for any reason, preventative measures should be taken to ensure that the critical areas or direct supporting areas are not contaminated.

11) Sterilized rubber closures and other components should be supplied from supporting areas in a manner that should maintain their sterility. To this end, the frequency of supply deliveries should be kept to a minimum.

12) The sterility of the filling process should be verified by process simulation. All operators engaged in sterile filling processing are required to participate in a process simulation at least once a year that should be conducted assuming the worst-case scenario. It is recommended that process simulation be conducted once every 6 months.

13) Equipment used in the filling process and areas where a filling operation has been performed should be subjected to an appropriate inactivation treatment if the pharmaceutical ingredients involved are physiologically active or contain potentially infectious microorganisms. Appropriate methods should be also employed to eliminate microorganisms present in exhaust air coming from filling operation area.

17.2. Powder

Powder filling process should be controlled as described in 17.1 "Liquid Products", in addition to the following items.

1) The maximum time permissible for powder filling procedures should be established and the adequacy of the time should be demonstrated via validation.

2) Bulk powder to be used in the filling process should be preserved in hermetic containers. It is acceptable to put the powder in other types of containers if there are alternate methods that have been proven effective in keeping the powder free from contamination with foreign matter and microorganisms.

3) Documented procedures for confirming the tightness of the container seal should be established. A schedule for gasket replacement should also be established.

4) The degree and type of airborne particulate monitoring to be performed during filling operations in an APA should be based on the requirements listed below (to be collected during validation procedures conducted under operating conditions with the HVAC system running). The criteria for the control of airborne particulate during the filling process should then be established based on these data.

   (A) Particulate level when powder filling machines are not being operated

   (B) Particulate level when powder filling machines are idling

   (C) Particulate level during the actual powder filling process (to be measured at the time of periodic validation for process control)

5) If the outer surface of containers is to be cleaned using compressed air (following the filling process), the dispersion of powder into the environment should be minimized by appropriate means.

6) Any aseptic operation exposed to the environment, such as the assembly of filling machines, the filling process of powder products, and the supply of rubber stoppers and bulk powder to hoppers, should be conducted in critical areas. The procedures for these operations and subsequent cleaning procedures should be established and noted in relevant SOPs.

7) The frequency of supply delivery of, for example, rubber stoppers and bulk powder, should be minimized.

8) Equipment used for the filling process and in areas where the filling operation is performed should be subject to appropriate decontamination treatment if the powder to be filled is physiologically highly active. Appropriate methods should also be employed for the elimination of such active substances in the exhaust air.

9) Filling and stoppering should be conducted in a critical area (Grade A). Cap sealing should be conducted in Grade C or higher area with additional protection if the degree of contamination risk warrants it. The time period between stoppering and sealing should be as short as possible.

10) The use of belt conveyors is not recommended for transporting materials between APAs and adjacent areas of lower cleanliness levels. When materials need to be moved to an APA from an area of lower cleanliness for any reason, preventative measures should be taken to ensure that the critical areas or direct supporting areas are not contaminated.

11) The sterility of the filling process should be verified by process simulation. All operators engaged in sterile filling processing are required to participate in a process simulation at least once a year that should be conducted assuming the worst-case scenario. It is recommended that process simulation be conducted once every 6 months.

18. Sterile Filtration Process

18.1. Liquid Products

18.1.1. Selection of Filters for Sterile Liquid Filtration

Manufacturers conducting sterile filtration should select filters based on their physicochemical properties, biological safety, and bacterial retention capacity. Filters should be evaluated based on compatibility with process characteristics, such as the components to be used, and the required membrane surface areas (determined based on documented evaluation programs or evaluation procedures). Generally, the nominal pore size of filters suitable for the filtration of liquid products is less than 0.2/0.22 μm.

18.1.2. Liquid Filtration and Process Control

Manufacturers conducting sterile filtration should identify and establish the process parameters necessary for liquid filtration based on the characteristics of the filters and drug products. The parameters established should be verified by validation.

1) Cleaning procedures

   The filtration system should be evaluated after the cleaning of filters, along with the down stream side of the filter assembly (e.g. piping and holding tank after filtering), to remove possible extracts, insoluble particulate matter, oxides, etc.

2) Filter sterilization procedures

   A procedure for sterilization of the filtration system should be established. It must be verified that all filters are being satisfactorily sterilized, but not damaged by the sterilization procedure. The maximum cumulative time of use under applicable sterilization conditions should be specified if the filters are sterilized and used repeatedly. Common sterilization procedures for filters include autoclaving, gas sterilization, and radiation sterilization.

3) Filter integrity testing procedures

   Filter integrity should be tested during day-to-day manufacturing processes by nondestructive means. It should be verified that the results from the integrity tests accurately correlate with the filter's ability to retain microorganisms.

(A) Filters should be moistened with a suitable wetting solution (recommended by the supplier) or the actual drug product that will be filtered through it.

(B) The SOPs for the integrity test should include, but are not limited to, the following:

(a) Procedures for filter wetting

(b) Environmental conditions for integrity testing

(c) Confirmation of the testing procedure

(d) Investigation of filter failures and trouble-shooting

(e) Record keeping

4) Filtration process conditions

The validity of the filtration process should be verified by taking the points listed below into consideration. Personnel responsible for the use of filters should perform validation procedures under operational conditions assuming the worst-case scenario.

(1) Compatibility of filters with drug products (e.g., chemical resistance), (2) maximum filtration time/maximum time of contact with drug products, (3) maximum filtration volume, (4) maximum flow volume, (5) temperature, and (6) maximum differential pressure

18.1.3. Validation of Filters for Bacterial Retention Ability

1) Bacterial challenge test

The ability of filters to retain bacteria should be validated under operating conditions assuming the worst-case scenario, e.g., maximum filtration volume and maximum differential pressure.

2) Challenge solutions and challenge microorganisms

(A) Challenge solutions

The solution to be used in the bacterial challenge test should be a solution of drug product that has been sterilized by filtration during an actual manufacturing process. If the characteristics of the challenge solution have to be modified for antibacterial potency evaluation or for some other reason, filtration processing should be conducted using drug solution under simulated operating conditions with actual manufacturing parameters in place in order to verify the compatibility of the drug substance and the filter. The challenge test should then be performed under modified conditions.

(B) Challenge microorganisms

Brevundimonas diminuta (ATCC 19146) or another scientifically justifiable microorganism should be employed to confirm that the filtration process generates a sterile filtrate. The challenge level should be 10^7 colony-forming units (cfu) of test organisms per cm^2, under actual process conditions.

18.1.4. Filtration System Design

The filtration system, consisting of pipes, valves, and instruments such as pressure gauges, gaskets, and filters should be designed keeping the physicochemical properties of the materials that come in contact with the drug solution in mind. Due consideration should also be given to minimizing the number of sanitary joints installed. The filters and their housings should be

designed so as not to retain air or condensed water which may generate cold spots during steam sterilization.

18.1.5. Routine Procedures

1) Cleaning of filters and filtration system

   Filters should be cleaned according to appropriate procedures established during the process development phase of the filtration system.

2) Sterilization of the filtration system

   In order to prevent microbiological proliferation, operators of equipment that utilize filters should sterilize the filtration system promptly after completion of the cleaning process using appropriate procedures established during the process development phase of the filtration system.

3) Filter integrity test

   A validated filter integrity test should be performed after filtration (after use of a filter) without dismantling the filter assembly. If process conditions permit, the integrity test should be also performed prior to filtration (before use of a filter).

4) Bioburden control

   Bioburden level of the drug solution prior to filtration should be checked.

5) Maintenance and change control

   Maintenance procedures for both the filters and the filtration system should be established and implemented, including test instruments. If the filter use or maintenance conditions change for any reason, such changes should be evaluated in detail prior to implementation, and recorded with justification, as appropriate.

6) Personnel training

   Appropriate training for operators who engage in the filtration sterilization process during manufacture should be conducted. Training topics should include, but are not limited to, operation procedures of integrity testing, procedures for investigating integrity test failures and implementation of countermeasures, procedures for filter and housing (if applicable) assembly and disassembly, and the cleaning and sterilization of filters.

7) Batch production records

   The filter operator should document and retain records of the following items (at the minimum) in the batch production record.

   (A) Filtration Procedures

   (B) Name and batch numbers of drug products filtered

   (C) Operator's names and signatures

   (D) Name of filter manufacturer, type, lot, and/or serial numbers

   (E) Cleaning and sterilization conditions for filters and the filtration system

   (F) Conditions for filtration processing (e.g., differential pressure, primary and secondary pressure, flow volume, operating temperature, and time)

   (F) Filter integrity test outcome and suitability determination

18.2. Air and Gases

18.2.1. Selection of Filters for Sterile Gas Filtration

Filters to be used in sterile gas filtration should be made of hydrophobic materials, and the selection of filters should be based on their physicochemical properties, biological safety, and bacterial retention capacity. The desired membrane surface area should be determined according to the requirements of each individual process, the required flow volume, and the differential pressure between processes. Generally, the nominal pore size of filters suitable for gas filtration is less than 0.2 μm.

18.2.2. Sterile Gas Filtration and Filtration Process Control

1) Procedures for sterile filtration

Since filters are generally used repeatedly, the maximum cumulative filter use time under applicable sterilization conditions should be determined. Common procedures for filter sterilization include using a SIP system, autoclaving, gas sterilization, or radiation sterilization. When steam sterilization is employed for filter sterilization, water could be retained in the filter, which would reduce the filtrate flow volume. Because of this, the length of the steam blowdown period should be sufficient to eliminate water from the filter, but should also be the shortest possible, in order to prevent the proliferation of bacteria.

2) Filter integrity testing procedures

A filter integrity test should be performed (using a non-destructive method) to verify the filter's microorganism-retaining capacity.

(A) Processes in which filtered gases come into direct contact with sterilized materials or products

When filters are to be used during a process in which filtered gases come into direct contact with sterile materials or products (e.g., in sterile filling machines, sterile bulk holding tanks vent filters, vacuum break filters of freeze-dryers, or autoclaves), the gas filtration filter integrity test should be positively correlated to the removal efficiency demonstrated by the bacteria challenge test (in general, the challenge test is implemented using water by the filter manufacturer). The filter integrity testing method should also be investigated in detail in consultation with the filter manufacturer (refer to Section 18.2.3).

(B) Processes in which filtered gases do not come into direct contact with sterilized materials or products

If the filters are used in a process during which filtered gases do not come into direct contact with the sterile materials or products (e.g., air supply during bulk intermediate product manufacturing process and fermentation process, the gas filtration filter integrity test should correlate positively to the removal efficiency demonstrated during the bacteria or bacteriophage challenge test under the conditions mentioned above (A) or using aerosol-challenge test methods. The filter manufacturer's integrity testing should also be investigated in detail (refer to Section 18.2.3).

3) Filtration process conditions

Filters for gas filtration should be selected after confirming a material's durability, including resistance to oxidation, since filters are generally used repeatedly and for a long period of time.

Also, the following gas filtration process parameters should be established (Validation of gas filters is not always required to each process since establishing of the process parameters in the worst case scenario is unrealistic for gas filters, but the gas filters used in the process in which filtered gases come into direct contact with sterilized materials or products should be positively correlated to removal efficacy demonstrated by bacterial challenge test. In general, the challenge test is implemented using water by the filter manufacturer): (1) temperature, (2) maximum pressure differential, (3) gas flow direction, (4) duration of use, and (5) frequency of filter sterilization.

18.2.3 Bacterial Retention Efficiency

Manufacturers conducting sterile filtration should confirm the applicability of the methods used and the results of the bacterial retention tests by referring to the filter manufacturer's certificate of analysis and validation support data.

18.2.4 Design of Filtration Systems

Condensed water, when accumulated on filters, could impair the flow of filtrate and permit proliferation of bacteria. The filtration system needs to be designed to eliminate condensed water from filters and their housings promptly after it appears. If the generation of condensed water is inevitable, as is the case with WFI tanks, certain preventive measures, e.g., heating the filter housing, should be instituted (refer to Section 18.1.4).

18.2.5 Routine Procedures and Validation

Gas filters can be evaluated to determine using liquids whether particles and/or fibers of filter material become detached when used during the manufacture of drug products, i.e., processes that permit the direct contact of filtered gas with sterile materials or products. In principle, the drug product manufacturer should evaluate the need or frequency of filter cleaning validation (CIP or cleaning prior to sterilization) based on data provided by the filter manufacturer (refer to section 18.1.5).

19. Freeze-Drying Process

19.1. General Requirements

1) When unstoppered vials or unsealed ampoules are exposed to the environment before being placed in a freeze-drying chamber, appropriate measures to prevent microbial contamination should be established while they are being transferred from the filling area to the freeze-drying chamber. Contamination should also be prevented while the vials or ampoules are being held in the chamber as well as during the period until sealing of the vials or ampoules is completed.
2) The area through which intermediate products will be transported into the freeze-drying chamber should be kept at the critical-area cleanliness level (Grade A). Some means to accomplish this include tunnel-type automatic transfer lines, transportation vehicles equipped with unidirectional airflow devices, and/or isolators.

3) A critical-area cleanliness level should be maintained while vials are waiting to be stoppered in the freeze-drying chamber or are being held in transport. The processes of ampoule sealing and the vial stoppering should be conducted in an environment maintained at the critical-area cleanliness level throughout the entire process.

4) For containers stoppered in the freeze-drying chamber, it should be confirmed that stoppers are placed deep enough to prevent leakage. The containers and closures should also be designed to maintain suitable air-tightness to minimize the risk of contamination and moisture absorption until sealing. Cap sealing should be performed in an area of Grade C or higher cleanliness level. Additional preventive measures should be taken, if warranted, depending on the level of contamination risk.

5) Microbial cleanliness should be evaluated in the areas where operations described in 2), 3), and 4) are performed.

6) The sterility of drug products after distribution to the market should be guaranteed by ensuring the integrity of the container/closure system based on validation, in-process control tests, and/or other testing.

7) The intrusion of air into the chamber from outside should be strictly kept at the minimum to ensure the sterility of the drug products during freeze-drying. Procedures for leak testing and those for ensuring the integrity of vacuum break filters and leak filters for controlling the vacuum level should be established.

19.2. Validation

1) Microbiological and physical monitoring programs should be established and validated for the freeze-drying process and other processes immediately before and after the freeze-drying process to assure sterility. The microbiological monitoring program is usually comprised of the media fill test or a process simulation test, bioburden control, and validation for sterilization of the freeze-drying equipment. The physical monitoring program includes leak testing and integrity testing of vacuum break filters and leak filters. Routine validations for the sterilization process, bioburden control, and filter integrity test, should be performed in a similar manner as for equipment used in the manufacture of sterile drug products.

2) The following procedures should be established as an important control program for the freeze-drying process. A process simulation test should be performed to verify effectiveness.

   (A) Transport of filled and partially stoppered containers into a freeze-dryer

   (B) Placement of filled and partially stoppered containers on shelves

   (C) Transport of intermediate freeze-dried products to the cap sealing process location

   A process simulation test should be performed by reproducing one of the following operating procedures actually employed during manufacture:

   (A) Direct manual operation

   (B) Mixed direct and indirect transport systems using manually operated or remotely controlled tray carriers

   (C) Fully automated loading and unloading systems

   (D) Isolator system (fully-automated or manually operated by personnel wearing a half suit)

3) The process simulation should be performed under simulated worst-case conditions. The worst case scenario should include, but not be limited to, the following parameters:

   (A) Solution to be filled, containers, and closures that have been stored in an aseptic process area longer than usual after sterilization should be used.

(B) The open area of the container should be the largest possible.

(C) The number of operators in an aseptic process area should be the largest permissible according to the relevant SOPs.

(D) The risk of contamination due to exposure to the environment should be maximized by filling the largest units at the slowest speed and by taking the maximum possible time up to the completion of transport of filled and half stoppered products to the freeze-drying chamber.

(E) A simulated troubleshooting operation and other applicable intervention procedures should be incorporated to simulate operations where unusual manufacturing conditions would occur, e.g. when containers are broken.

4) The freeze-drying process simulation test should be conducted after determining appropriate conditions (referring to actual manufacturing programs) that will not interrupt the growth of microorganisms nor impair the growth promotion activity of culture media.

(A) Appropriate temperature and cooling time should be specified.

(B) The pressure reduction should be gradual and not so great as to cause boiling or spontaneous freezing.

(C) The freeze-drying program, in particular drying time, should be established so as not to encourage the drying of culture media nor impair the growth promotion activity of culture media.

(D) Simulations of freeze-drying processes should be conducted and preferably repeated several times using the worst-case conditions, which should include, but are not limited to, the following:

Unfavorable turbulence when pressure reduction is begun, at the time of vacuum break, or when intermediate products are loaded, and operations associated with a high risk of microbiological contamination due to personnel intervention

(E) Some of the containers of the freeze-dried product are filled with an inert gas, such as nitrogen, to ensure the stability of products to be preserved. When soybean-casein digest (SCD) agar medium is used, air should be used instead of inert gases to meet predefined growth conditions for aerobic microorganisms. When anaerobic microorganisms are confirmed or suspected to be present on the medium, inert gases, instead of air, and growth media for anaerobic microorganisms (e.g., fluid thioglycollate media) should be used.

(F) The freeze-dryer should be loaded to full capacity with media units when the capacity of the freeze dryer is less than or equal to the standard 5,000 units of media. When the capacity of the freeze dryer is more than 5,000 units of media, containers filled with media should be placed at appropriately selected locations within the freeze-dryer; that is, the containers should be randomly placed or evenly placed to permit evaluation without bias. Containers filled with media may be placed in locations where the risk of contamination is high if the simulation is intended to test the possibility of contamination under the worst-case conditions, such as leakage with breached filter integrity, leakage from doors or cold trap, or back-diffusion of gas or air from a vacuum pump.

5) The integrity of containers and closures should be validated to ensure the sterility of drug products after shipment.

6) The validity of the freeze-dryer leak test, the integrity of vacuum break filters and leak filters, and the degree of vacuum involved should be validated to verify that outside air does not enter the freeze-dryer under negative pressure. The judgment criteria for the leak test should be established so as to minimize the risk of microbial contaminating of the freeze-dryer. The

following factors should be taken into consideration: freeze-dryer chamber volume, amount of time spent under reduced pressure during the freeze-drying process, and the bioburden carried by the air around the freeze-dryer.

19.3. Cleaning and Sterilization of Freeze-dryers

1) The following should be taken into consideration when cleaning freeze-dryers:
   (A) Cleaning procedures should be established with due awareness of the difficulties involved when cleaning freeze-dryers, which have a complex inner structure.
   (B) It is recommended that the cleaning efficacy be verified by not only sampling the rinse water, but also by using the swab method to collect samples from the backs of shelves and near drains. The sticky tape transfer method is also effective for sampling.
   (C) The toxicity of cleaning agent residue should be evaluated by analyzing samples collected by appropriate methods, such as the swab method or rinsing. The adequacy of evaluation methods should be also verified.
2) Appropriate procedures should be established and validated to ensure the sterilization of freeze-dryers.
   (A) The freeze-drying chamber should be sterilized with enough time to ensure complete sterilization due to possible cold spots. An extended sterilization period is also desirable because of the time required for sterilizing gas to diffuse through the complex inner chamber made of various materials, and, because in the case of sterilizing gas, variations in temperature and humidity are inevitable within the chamber. Gas circulation and diffusion patterns should also be evaluated in detail.
   (B) Since the inner structure of the chamber is so complex, steam sterilization of the freeze-drying chamber should be performed with due care for the efficient displacement of stagnant air and the removal of condensed water.
   (C) Basically, steam sterilization should be conducted following every freeze-drying batch. When the sterilization interval is changed in accordance with the properties of the products to be freeze-dried, or for other reasons, the changes should be validated microbiologically.

19.4. Routine Monitoring and Control and Maintenance of Freeze Dryers

1) Freeze-dryer integrity should be tested according to the procedures listed below. Caution should be taken to identify pseudo-leaks of gas that occur inside the freeze-dryer.
   (A) Leak test for every batch of freeze-drying process

   Records of the leak test data should be documented in brief upon completion of the freeze-drying process.
   (B) Leak test upon completion of steam sterilization

   Records of the leak test data should be obtained after cooling of the freeze-dryer since steam sterilization places significant stress on the chamber.
   (C) Leak test as part of periodic revalidation

   At the time of periodic revalidation, or for other types of evaluations, the freeze-dryer should remain empty overnight under reduced pressure in order to measure the actual leakage of the equipment.

(D) An additional leak test should be performed promptly when any abnormal findings are obtained during the leak tests [(A) and (B)] listed above.

2) The periodic diagnostic function test program should include, but not be limited to, the functional diagnosis of the shelf heat transfer/circulation system of shelves, the cooling system with 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 the cumulative time or frequency of use.

4) Critical monitoring instruments and freeze-dryer controls, such as the temperature and vacuum gauges, should be calibrated periodically and the calibration results should be documented. A calibration interval of approximately 6 months is recommended, unless previous calibration results suggest a more appropriate interval.

5) Vacuum gauges are highly sensitive meters used for the measurement of very minute changes in pressure, and it is practically impossible to calibrate them in place. It is recommended that calibration be contracted out to an authorized organization for calibration by a method having traceability.

20. Other Aseptic Manufacturing Equipment

20.1. Isolator Systems

Isolator systems for the manufacture of sterile drug products are made up of equipment and devices that are capable of maintaining a highly aseptic environment by minimizing the area for aseptic processing and by eliminating personnel as a source of contamination from the critical processing area. Sterile drug products with highly active pharmacological properties are manufactured using an isolator system where the cabinet is maintained under negative pressure. However, sterile drug products are usually manufactured by using an isolator system that is operated under positive pressure.

Properly designed isolators provide a high level of integrity, but the cabinet does not provide an absolute seal. It is critical to prepare a comprehensive preventive maintenance programs for gloves, half suits, and various sealing parts.

20.1.1. General Requirements

1) The air cleanliness level of the environment where isolator systems are installed for the manufacture of sterile drug products needs to be at least Grade D.

2) Ports used for connecting two isolators or transfer ports for the aseptic loading/unloading of materials should be designed to be structurally suitable for maintaining the integrity and sterility of the isolators.

3) The number of half suits, gloves, transfer ports, and connection ports should be kept at a minimum in order to reduce the chance of contamination.

4) The design of transfer ports for the loading and unloading of finished or half-finished products should be suitable for preventing invasion of potential outside contamination sources. The port should be also suitable for maintaining an appropriate pressure difference.

5) The efficacy of the decontamination of the inner surface of the isolator system using a suitable disinfectant should be verified biologically by confirming a 4-6-log reduction of a test

organism known to be resistant to the disinfectant used. The degree of decontamination necessary should be established based on the intended use of and bioburden for the equipment in question. It should also be verified that the materials and equipment to be used for manufacturing should achieve a 4-6-log reduction of organisms prior to entry into the isolator system. A 6-log reduction does not mean a complete kill of the biological indicator with a population of 10^6.

6) It should be verified that the microbial load of any surface that may come into contact with the drug products has been reduced by log 6 or greater.

7) The leak test should be performed according to predetermined criteria.

8) The decontamination frequency should be established based on validation data.

20.1.2. Air Conditioning System

1)The rate of air exchange inside the isolator system should be adequate to prevent the retention of particulate matter or other contaminants. It should also be sufficient to prevent an increase in temperature over the predetermined limit.

2) Air velocity and airflow pattern should be adequate to maintain the cleanliness level required for the operations inside the isolator system.

3) Batch production may be performed under turbulent airflow conditions if a small closed-system isolator with a simple inner structure is used. However, the airflow should be unidirectional when a continuous transfer port is used for loading and unloading purposes.

4) The cleanliness level of air inside the isolator system should meet the specifications predetermined by the user.

5) Air in the isolator system should be circulated through a HEPA or higher-grade filter. Any exchange with outside air should also take place through a HEPA or higher-grade filter.

6) Isolator systems should be capable of maintaining an appropriate manufacturing process-specific pressure difference between the isolator and the surrounding environment where it is installed. The difference should be maintained at a minimum of 17.5 Pascals when the isolator is installed in a Grade D area. A greater difference may be necessary depending on the type of operation and when, for instance, half suits and gloves are used during operation. Pressure differences should be continuously monitored and recorded throughout operation. An alarm system should be installed to warn operators of an abnormal drop in pressure.

20.1.3. Decontamination

1) A decontamination process should be established and routinely implemented. The following should be taken into consideration:

   (A) Cleaning and drying of the internal surfaces of the isolator system

   The internal surfaces of the isolator system should be cleaned and dried, as required, prior to decontamination. Cleaning agents, if used, should be compatible with all materials of construction, and a residue test similar to the ones used for cleaning validation should be performed.

   (B) Biological indicators

   (C) Chemical indicators

(D) The temperature both inside the isolator and in the surrounding environment (including temperature mapping)
(E) Humidity
(F) Time of exposure to decontaminants (duration of decontamination)
(G) Concentrations of decontaminants
(H) Pressure difference
(I) Diffusion of decontaminants to the entire inner surface of the isolator
(J) Bioburden

2) Decontaminants should be selected after evaluating compatibility with the isolator system's materials of construction, the type of operations to be performed, the volume and configuration of materials inside the isolator, as well as the bioburden. Common decontaminants include peracetic acid vapor or mist, ozone gas, and chlorine dioxide gas, as well as hydrogen peroxide vapor.
3) The decontamination should be performed by personnel who have sufficient knowledge and understanding of the characteristics of decontaminant mist, vapor, or gas and the operation of the generator of these agents.
4) Care should be taken so that decontamination operations have no adverse impact on operators, i.e., the concentrations of the decontaminants meet the work environment criteria for the room where the isolator system is located.
5) The composition and identity of the decontaminants should be checked before use to ensure that they meet predetermined criteria.

20.1.4. Personnel Training

The training program for personnel who engage in the operation of isolator systems should include the following items (at the minimum):

(A) Proper use of gloves and/or half suits
(B) Decontamination of the inside of the isolator system
(C) Isolator system integrity testing
(D) Loading of materials and unloading of finished or half-finished products
(E) Operation, monitoring, and maintenance of the isolator system
(F) Safety management of decontaminants based on the Material Safety Data Sheet (MSDS) and compatibility of decontaminants with the isolator system
(G) SOPs specific to each process

20.1.5. Routine Monitoring and Control

Routine control requirements for the isolator system should include the following items (at the minimum):

1) Operating procedures should be prepared based on validation data.
2) Isolator systems are considered to maintain a high level of integrity, but the integrity is not always perfect. Therefore, leak tests should be performed at regular intervals in addition to

prior to each decontamination cycle. Leak test methods should include, but are not limited to, the following:

(A) Pressure hold test

(B) Gas detection method

3) Gloves should be checked visually for tears or any other damage at each use.

4) A physical leak test should be performed on gloves, and microbiological monitoring using the swabbing method should also be performed on a regular basis.

5) A preventive maintenance program should be developed to specify the replacement schedule for degradable materials.

6) Decontamination process parameters such as temperature, humidity, and gas concentration should be monitored and recorded at predetermined locations during each decontamination cycle.

7) The particle count inside the isolator should be monitored at predetermined locations and at suitable time intervals.

8) Microbiological monitoring should be conducted at predetermined locations and at suitable time intervals based on validation data. Example locations for monitoring include the inner surfaces of the isolator system, surfaces of gloves, materials placed inside the isolator system, and the material contact surfaces.

20.2. Blow-Fill-Seal (BFS)

20.2.1. What is Blow-Fill-Seal?

The blow-fill-seal (BFS) is a specialized aseptic packaging technology using in-line forming, filling, and sealing of sterile plastic containers using plastic pellets. Since plastic containers are molded, filled, and sealed in a continuous production run under a closed and sterile environment, the sterility of drug products can usually be assured without terminal sterilization processing following sealing (e.g., steam sterilization). Operations are carried out as a closed, automatic, and continuous process; hence, BFS is efficient for production and features little chance of contamination during production.

20.2.2. Scope of Blow-Fill-Seal and Processes to be Addressed

The types of sterile drug product manufacturing to be covered by the BFS process include the aseptic filtration of drug solution, loading of plastic pellets, molding of the container, filling of the drug solution into the container and sealing of the container for liquid drug products,. For powder drug products, loading of sterile powder, loading of plastic pellets, molding of the containers, filling of the sterile powder into the container and sealing are included.

This guideline covers the BFS which does not require sterilization following filling and sealing (e.g., steam sterilization). Special attention should be paid to the following:

1) Elution of plasticizers, additives, or residual monomer from plastic containers

2) Bioburden of plastic pellets

3) Environmental condition for plastic container molding

4) Assurance of sterilization of a drug solution (sterile filtration of a drug solution),

5) Compatibility of containers with drug solution

6) The cleanliness level of the environment in which the filling processing takes place, as well as the location where the equipment is installed
7) Sealing processing
8) Need for sterilization following filling

It is necessary to meet stringent criteria concerning the above points 2) the bioburden of plastic pellets, 3) the environmental conditions for plastic container molding and the cleanliness of the inside space of the molded containers, 6) the cleanliness of the filling environment, and 7) the sealing process and evaluation method for the sterility of drug products. This stringency is in order to strictly control and ensure the sterility of the manufacturing process and the final drug product.

20.2.3. Process Flow for Container Molding and Filling, and the BFS system Environment

1) Critical processes
   (A) Preparation of drug solution
   (B) Sterile filtration
   (C) Temporary storage
   (D) Molding (including clean air supplied into in the molding environment)
   (E) Filling
   (F) Sealing
2) Characteristics of the BFS system
   (A) All processes, from the molding of plastic containers to the sealing process, should be performed in a continuous automatic operation.
   (B) Filling and sealing processes should be carried out in a small isolated space. Therefore, a so-called Grade A aseptic "room" is not required, but a "small space" for molding and filling processing could be utilized and such space should be maintained at a Grade A cleanliness level. It is critical that the procedure for controlling air cleanliness in the small space for molding and filling processing be established correctly. The equipment for filling and sealing may not necessarily be installed in an aseptic area, or operators may not be required to wear a gown for sterile processing, if CIP and SIP systems can be applied to the manufacturing processes that follow the sterile filtration of a drug solution, (e.g., temporary storage, molding of plastic containers, filling of a drug solution, and sealing of containers). It is recommended that the environment be maintained at a Grade C cleanliness level in order to protect the drug products from contamination by foreign and particulate matter.

20.2.4. Sterility Assurance of Containers: Sterility Assurance of Plastic Pellets and Inner Surface of Molded Plastic Containers

1) In the BFS system, the inner surface of the molded plastic containers needs to be sterile. The following conditions [2) to 3)] must be met in order to maintain the sterility of the inner surface of the containers.
2) The molding process should be managed under the condition of dry heat sterilization to efficiently eradicate microorganisms (plastic pellet fusion and molding processes are