water-free, dry-heat states) or plastic pellets should be maintained in a condition free of the microbial contamination.

3) The temperature and time should be well controlled throughout the melting and molding processes because they are critical parameter not only for molding the containers, but also for killing the microorganisms present on the plastic.

4) The molding and filling processes and the processing environment should be validated via media fill simulation.

20.2.5. Sterility Assurance of the Product Filling Process: Procedures for Media Fill Simulation

Molded plastic containers made by the BFS process are maintained sterile by means of the following conditions;

1) When the melting and molding process satisfactorily meet the conditions for overkill, molded plastic containers are understood to be sterile. If the conditions for overkill are not satisfied, sterility of the container shall be assured by the following measures.

2) Sterility shall be assured by means of either the sterility of plastic pellets or the process of melting and molding.

3) If the melting and molding processes do not satisfactorily meet the conditions for overkill, and raw material plastic pellets are not sterile, a challenge test using standard microbial spores shall be performed to show that the melting and molding processes effectively kill spores. These measures provide assurance of the sterility of plastic containers.

Note: The Japanese, US, and European Pharmacopoeias recommend the use of *Bacillus atrophaeus* as an indicator for dry heat sterilization. The D_{160} value (160°C) 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.

20.2.6. Critical Control Parameters for the BFS Process

The critical control parameters for the BFS process are as follows:

1) Bioburden of plastics (in particular, fungi):

The sanitary state of the plastic materials and additives used for the manufacture the plastic pellets, and of their manufacturing process, should be confirmed and approved beforehand. If the information on these materials provided by the vendor is not sufficient, adequate attention should be paid to the sanitary state of the plastic before use.

2) The temperature for melting plastic pellets and the duration from melting to the plastic injection process for molding should be controlled.

3) The process of drug solution preparation and the drug solution transportation line should be adequately equipped with CIP and SIP systems to ensure the sterility of the drug solution preparation process and the drug products. If CIP and SIP systems are not available, certain off-line control systems should be in place to attain a similar quality of cleanliness and sterility.

4) Quality of air in the environment

When BFS technology is employed, drug products are exposed to the air during the molding and filling processes. The environment of the molding and filling areas and the air supplied to these areas should be monitored to maintain a level of Grade A air cleanliness.

The quality of air around the equipment should be level of Grade C or D cleanliness. Operators should wear gowns suitable for these cleanliness levels. However, the gown may not be required to be sterile, and sterility checks may not necessarily be required.

5) Two types of plastic container molding methods and air quality are used.

(A) Compressed air is injected to blow melted plastic into shape

(B) Melted plastic is suctioned from the outer surface and molded to a shape by vacuum

The latter method is more desirable because the container can be molded without introducing a larger amount of air into the mold and the inner surface of the container. In either case, air contacting the inner surface of the container should be free of microbes and_any other contamination and be controlled for dew point and microbial and particulate matter count (equivalent to Grad A air quality).

6) Air in a local space where the filling operation is performed should be maintained at the Grade A level and monitored continuously.

7) Heat transfer medium for heating and quality of products

Although it is unlikely that the heat transfer medium would come into direct contact with the molded plastic containers, pure steam should be used as a precaution against the possibility of accidental contact with the melted plastic or molded containers.

8) Heat transfer medium for cooling and quality of products

Although it is unlikely that the heat transfer medium would come into direct contact with the molded plastic containers, due attention should be paid to possible leakage or contamination of the melted plastic with the medium.

9) Seal integrity

Seal integrity is a highly critical parameter for the BFS process. Various methods have been developed to test the integrity of the seal, such as the inert gas detection method, high voltage detection method, and others. Seal integrity should be ensured by an appropriate method, and the reliability of the method should be verified.

10) CIP and SIP of the BFS process (temperature, time, and F_H)

The F_H value measures equivalent time to reduce the number of microbes, which have Z-value of 20K, to one tenth (1/10) by dry heat at 170 °C.

11) SIP of the filling process and seal integrity

12) Various challenge tests for manufacturing processes

13) Simulation of filling process (media fill)

14) Continuous operation (verification of the specified maximum continuous processing time)

The BFS process is often operated continuously, with no break. The maximum time allowable for continuous processing should be established and specified. Also, procedures and process parameters should be specified and followed for resuming processing after interruption or a break in operation.

21. Process Simulation Procedures

21.1. Process Simulation: Outline and Scope

Process simulation is the technique of applying the "media fill test" concept to all aseptic processes. Sterile drug products are manufactured using complex processes such as multiple aseptic processes or sometimes handling of sterile raw materials, and the aseptic filling process is only a part of these complex processes. All of the aseptic processes need to be validated in order to verify their appropriateness and effectiveness. Process simulation is a process validation method used to evaluate not only the aseptic filling process, but also the overall aseptic manufacturing processes. In this method, the product to be filled is replaced by either a microbial growth medium or some other substance that can support the growth of microbes. Process simulation can be applied to all manufacturing processes, including the aseptic preparation of sterile bulk drugs consisting of "filtration," "crystallization," "drying," "milling," "mixing," and "freeze-drying on trays to obtain a powder" as well as aseptic manufacturing processes for finished drug products such as "filling" and "sealing." In addition, the personnel who engage in these operations should participate in process simulations under actual processing conditions using actual operational procedures and actual environmental parameters under worst-case conditions.

21.2. Process Simulation Procedures

21.2.1. Size of Process Simulation Runs

In general, 5,000 units (gram or number of containers) should comprise a simulation size for one production run.

21.2.2. Media and Incubation Conditions

Process simulation tests should utilize sterilized media or powder sterilized via radiation (lactose, D-mannitol, polyethylene glycol, etc.) as the dummy substance.

Liquid media should be tested by indicator organisms (*) to verify that the material to be filled does not inhibit bacterial growth prior to (or concurrently with) incubation.

Powder media or dummy powder should be tested by indicator organisms (*) to verify that the liquefied media or the material dissolved in the media does not inhibit bacterial growth during incubation. The optimal concentration of the dummy media should be established (taking the osmotic pressure of the solution into consideration) and documented.

(* Indicator: Use microorganisms listed in the "Growth Promotion Tests" portion of the Sterility Test section of the Japanese Pharmacopoeia.)

21.3. Points to Consider for Process Simulation

Aseptic processes possess the potential for contamination, not only in the filling process, but also in other processes; therefore, all processes that could possibly introduce contamination should be tested. It is critical that all latent factors and elements that could cause contamination in routine procedures be examined, and all those identified by such examination be included in the process simulation.

The items listed below should be taken into consideration when performing a process simulation, in addition to the "Media Fill Test" described in the General Information section of the Japanese Pharmacopoeia.

1) All kinds of permissible interventions that could occur during aseptic processing should be simulated.
2) The duration of process simulation should be sufficient to cover most of the operations to be performed during the actual manufacturing process. The following factors should be considered.
   (a) Interventions of operations that may be presumed to occur during actual production
   (b) For the personnel involved: each employee's name or identification assigned to the process, and level of training
   (c) Supply of sterile raw materials, rubber stoppers, etc.
   (d) All working shifts and operators involved
   (e) Line speed (simulating conditions that would be most likely to cause contamination)
   (f) Process controls to be performed during processing
   (g) Container size
3) Process simulation should be performed under operating conditions that simulate the biggest and worst possible intervention conditions, including recovery from line damage, replacement of equipment parts for aseptic operation, or replacement of line filters, etc. The largest number of personnel that could possibly be involved in these operations should also be taken into consideration.
4) The time for process simulation should be designed by considering the longest possible actual operation time, and by taking all possible events into consideration.
5) Any additional possible interventions that could occur during routine aseptic processing should also be taken into consideration.

21.4. Evaluation

Evaluation of Process Simulation Results

As a rule, no positive results should be obtained from process simulation testing. The evaluation of results from the filling process simulation should be based on the acceptance criteria of the "Media Fill Test" listed in the General Information section of the Japanese Pharmacopoeia.

ANNEXES

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

A1.1 General Requirements

This section addresses issues necessary for the control of APIs manufactured by cell culture/fermentation in addition to the other regulations, guidelines/guidance, and precautions mentioned in the main text of this guidance.

1) The term "classical fermentation" refers to processes that use microorganisms existing in nature and/or those modified by conventional methods to produce APIs. The term "biotechnological process" refers to the use of cells or organisms that have been derived or modified by recombinant DNA, hybridoma, or other technologies to produce APIs. The control of microorganisms is usually more strict for biotechnological processes that produce proteins or polypeptides than those for classical fermentation processes.

2) Raw materials (e.g., media and buffer components) used in API production via cell culture/fermentation may be good substrates for growing microbes and thus invite contamination. Adequate process control parameters for raw materials, such as bioburden limits, should be established taking the following into consideration: the supplier, method of preparation, type and characteristics of the drug substance to be produced, and the production processes. Media or other materials used in cell culture/fermentation should be also monitored to detect *Mycoplasma*, etc., as appropriate.

3) The cleanliness level of the cell culture/fermentation processing areas should be established and controlled depending on the type of drug substance produced as well as the type of operation. The processing area where equipment and apparatuses are located, if they are part of a closed system, does not have to be maintained at a critical cleanliness level; however, the cleanliness of the area needs to be adequate to prevent the contamination of other materials.

4) Viral safety concerns should be managed as described in ICH guideline Q5A "Quality of Biotechnological/Biological Products: Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin."

5) In relation to in-process control and quality control (and monitoring of critical processes), any equipment sterilization or environmental microorganism monitoring records, etc., and

any deviations from specifications should be recorded for the purposes of microorganism control.

6) Restriction of personnel entry, clothing criteria, and sanitation practices (including health habits) in the cell culture/fermentation processing areas should be established, and personnel should be trained according to these criteria, as appropriate.

A1.2 Cell Culture/Fermentation

1) Appropriate operating and control procedures should be established and implemented to prevent the contamination of starting materials, such as working cell banks, that will be used in cell culture/fermentation.

2) Whenever feasible, equipment should be used in a closed or contained system in order to facilitate the aseptic addition of cell substrates, media, buffers, and gases. If the inoculation of the initial vessel or subsequent transfers or additions (e.g., media and buffers) are performed using open vessels, there should be operating and control procedures for minimizing the contamination risk.

3) Critical process control parameters such as cell growth, viability (in cell culture), and productivity should be monitored for effects caused by infections from bacteria, fungus, or *Mycoplasma*, etc.

4) If the equipment is designed to continuously supply media to a culture vessel and continuously discharge culture solution from the vessel during cell production, appropriate operating procedures should be established to maintain optimal conditions for cell culture within the vessel in question throughout the incubation period.

5) When used in the production of biotechnology products, cell culture and fermentation equipment should be cleaned and sterilized after every use. Fermentation equipment used in classical fermentation processing should be cleaned and sanitized appropriately. Procedures for cleaning cell culture and fermentation equipment should be established taking the characteristics of the equipment into consideration. In addition to CIP and SIP, other cleaning methods, such as disassembly for cleaning, and manual cleaning, etc. should be conducted as appropriate, taking the structural characteristics of the equipment into consideration.

6) Culture media should be sterilized by an appropriate method before use.

7) There should be appropriate written procedures for handling contamination, which describe contamination detection and the course of action to be taken. Procedures for the assessment of impact of the contamination on the product, and those for the decontamination of the

equipment and recovery to acceptable conditions for the use of subsequent batches should be included.

8) Biotechnological processing using open vessels should be performed in a biosafety cabinet or similarly controlled environment to prevent contamination, as appropriate. These control measures should take the following into consideration: contamination (biohazard) prevention for both personnel and the environment, and prevention of production process contamination.

A1.3 Harvesting, Isolation, and Purification

1) Harvesting steps, either to remove cells or cellular components or to collect cellular components after disruption, should be performed in areas and using equipment designed to minimize the risk of microbial contamination to the harvest, environment, and personnel.

2) If open systems are to be used in the purification process, purification should be performed under clean environment conditions appropriately controlled for the preservation of intermediate product quality.

3) Processes that remove or inactivate the producing organism, cellular debris, or media components should at the same time minimize degradation, contamination, and loss of quality, and should be adequate to ensure that the intermediate or API is recovered with consistent quality.

4) Buffers, column chromatography equipment, and other equipment used in the purification process are not necessarily required to be sterile, but the presence of microorganisms should be within acceptable levels that will not affect product quality. The levels to which microorganisms must be controlled may vary depending on the time, temperature, and pH, etc. necessary for the purification processes. When necessary, endotoxins should also be measured.

5) All equipment should be properly cleaned and, if necessary, sanitized after use.

6) Purified intermediates should be sterilized by filtration or other appropriate methods before storage, or the levels of microorganisms should be controlled appropriately during storage.

A2. Pharmaceutical Waters

Water used in the manufacture and processing of pharmaceutical materials and products, the washing of vessels, containers, and equipment, and that used for the preparation of

pharmaceutical solutions is called pharmaceutical water. Water is an excellent solvent as well as being essential for the growth of microorganisms. This means it could be a source of impurity as well as invite the proliferation of microorganisms. Inappropriate water control may promote these conditions in the water supply system and, when passed on to drug products, could pose serious and unexpected risks to the users of the products. It is critical that the quality of pharmaceutical water be ensured by establishing suitable hardware and software systems to prevent contamination, validating the system to provide the required quality of water consistently, and verifying the quality through routine monitoring and control. This guidance describes the basic concepts applicable to the manufacturing control and quality control of pharmaceutical water.

A2.1 Basic Designs of Facilities, Equipment, and Systems Applicable to Pharmaceutical Water

The basic design of the facilities, equipment, and systems applicable to pharmaceutical water should be developed after establishing intended procedures of operation and control of the facilities and equipment, manufacturing control, and quality control in order to constantly prepare the required quality of pharmaceutical water. Critical points to consider in designing these water systems should include, but are not limited to, the following:

1) The design should be based on predetermined specifications, production volume, and control systems for pharmaceutical water.
2) The design should be developed taking the quality of the source water, including seasonal changes, into account.
3) The design should be able to supply water of an acceptable quality and in the amount required according to the maximum values for the following parameters: volume of consumption in a unit of time, duration (time) of use, frequency of use, and various conditions to be established at the point of use (e.g., temperature, number of use points, piping specifications).
4) As a rule, equipment that cannot be sterilized with chemical agents or by other means should be designed as a circulating loop system. However, it is recommended that equipment have a sterilization or disinfection system to ensure microbial control.
5) The position of the sampling port, when required, should be evaluated during the design stage and should be positioned as close as possible to the water treatment equipment installed for each purification process that requires water quality test.

6) Filters should not be used at any point within the water piping for pharmaceutical processing or that for the final rinse of the container closure system or pharmaceutical manufacturing equipment.

7) Measures to prevent the backflow of water should be in place at joints connecting different types of equipment.

8) A sanitary pipeline with detachable joints composed of austenitic stainless steel (e.g., AISI 316, AISI 316L or equivalent grade) appropriate for the above-mentioned sterilization process should be used, except when the pipeline is positioned next to equipment or valves that are to be detached for supply or replacement.

9) The entire pipeline should be installed at an angle to allow for the complete drainage of water from the system.

10) The length of any dead legs should not be greater than 6 diameters of the unused pipe, starting from the joint of the pipe in active use.

A2.1.1. Pretreatment Equipment

Pretreatment equipment should be selected and designed to adequately identify and remove materials or particles that could be present in source water, maximizing equipment treatment efficiency and prolonging the length of time it may be used to supply water at a quality level greater than that required. The selection of the equipment should be based on due review and investigation of its potential to detect signs of contamination and how it should be cleaned if contamination should occur. Also, the negative effects of heavy metals, free chlorine, organic matter, microorganisms, and suspended and colloidal particles on the performance and life of the equipment should be evaluated and minimized.

A2.1.2. Equipment for Production of Water for Injection

Since water for injection needs to be microbiologically pure, the equipment used for its production should be capable of withstanding periodic sterilization with pure steam at temperatures over 121°C for a given length of time. If steam sterilization is not possible because of low heat tolerance, an alternative sterilization or sanitization procedure (e.g., hot water or chemical agents) should be used for the equipment. The points to take into consideration when selecting equipment to be used for the production of water for injection are listed below.

1) Water Distillation Equipment

Distillers can be used to fractionate vapor into high and low boiling point and mist components by physical processing of separation, removal, or condensation, which separates the impurities and produces chemically and microbiologically pure water. There are three types of distillers that are commonly used: single-effect stills, multi-effect stills, and vapor-compression stills. The latter two types are capable of producing a large quantity of high quality water. They are also highly energy efficient and are thereby recommended for large-scale water production. Each of these three types of distiller has different characteristics, and it is important to make a selection based on the intended use, design, and specifications of the water system in order to fully utilize the advantages offered by each one.

The design of the water system should include, but not be limited to, the following considerations: a pretreatment system for the feed water, as required (e.g., ion-exchange, reverse osmosis, and/or ultrafiltration), preventive measures against contamination caused by source water particles carrying impurities, measures for dissolving minerals deposits left by hard water, confirmation of adequate water drainage, prevention of backflow into distillers from their respective collective drainage canals, and prevention of contamination of heat exchange media with cooling water or heating steam.

2) Reverse Osmosis (RO)

Reverse osmosis (RO) uses a semipermeable membrane to allow water to move across the membrane against the osmotic pressure. This improves water quality by reducing the levels of such small molecular substances as inorganic salt, as well as solvent molecules, microorganisms, endotoxins, etc. The advantages of RO treatment outweigh those of distillers in that the treatment can be performed at room temperature and is cost effective; however, stricter control is required to prevent pinhole leaks in the membrane and microbiological contamination. Points to consider when using RO treatment are listed below:

1) Carbon dioxide and ammonia gas should be removed from feed water by deaeration, neutralization, or ion-exchange prior to RO treatment, since these gases cannot be removed by RO.
2) RO has a limited capacity to remove endotoxins from water. It is recommended that appropriate procedures for monitoring and controlling the microorganism count in the pretreatment stage be implemented to ensure that the quality of feed water is within the capacity of the RO system.

3) Generally, RO treatment is performed at room temperature, and, in view of the membrane structure, there is a possibility of microbiological contamination on the downstream side of the membrane due to pinhole leaks. It is recommended that the system structure be designed to consist of at least two RO modules in series to provide enhanced reliability and greater control. Additionally, UV sterilization, heat-treatment, and other effective means should be exercised to prevent microbial growth downstream of the filter.

4) Microbiological growth inherent to operations at ordinary temperatures should be controlled via validated chemical treatment or hot water sterilization using a heat-resistant RO system.

When water purified by RO is used as water for injection, it must be verified by routine practice of validation, monitoring, and control that the water is constantly produced and supplied in a quality equivalent to distilled water.

3) Ultrafiltration (UF)

An ultrafiltration (UF) purifier, which is frequently used to produce pharmaceutical water, is a kind of hyperfiltration apparatus capable of removing endotoxins from feed water. Some UF units, unlike RO, can be operated without high pressure and are resistant to heat and steam sterilization, making them easy to sterilize with high temperature water or chemical agents. It is recommended that the UF unit be capable of removing organic substances with molecular weights from 6,000 to 10,000. The purification performance of a UF unit, like RO, is dependent on the upstream water quality and design of each system. In addition, routine maintenance and control should be instituted to minimize the influence of microorganisms retained and growing on the membrane filters along with particulate matter on water quality and the water production capacity of the system.

When UF is used in water for injection systems, it must be verified, by validation and routine monitoring, that the water is produced and supplied at a constant quality level equivalent to water produced by a distiller.

4) Holding Tanks for Water for Injection and Other High-purity Waters

It is desirable that pharmaceutical water to be used in the manufacture of sterile drug products be used promptly following production to avoid microbial contamination or chemical deterioration. However, the amount of water produced does not usually coincide with that

actually used in manufacture. Because of this, water may be kept in a holding tank until use. Points to consider in designing the holding tank are listed below.

1) The holding tank should be closed-type units with smooth inner surfaces. The number and length of projections from the tank as well as the number of ports should be kept to the minimum and be as short as possible.

2) The structure of the storage tank should be designed to prevent stagnation and to facilitate complete drainage. The inner surface should be easily cleanable.

3) Since water deteriorates when stored in a tank for a long period of time, the size of the storage tank should be suitable to prevent excessively long retention of water.

4) The holding tank should be equipped with 0.2-μm hydrophobic vent filters to prevent entry of microorganisms and impurities from the outside.

5) The holding tank should be equipped with mechanisms that distribute heat to the entire inside of the tank, including the upper portion, to achieve adequate hot water sanitization.

6) It is desirable for the holding tank to be equipped with an alarm to signal the rupture of the rupture disc valves so that the integrity of the stored water may be maintained.

7) Microorganisms grow readily and erosion tends to occur in the tank at the meniscus. It is recommended that water circulate continuously on the exposed inner surface of the entire tank, including the upper portion.

5) Piping

The pharmaceutical water in a holding tank is transported to use points through pipelines. The pipes are relatively small in diameter and arranged as a closed system. Once installed, the inside of the pipes is difficult to inspect. It is critical to thoroughly evaluate procedures for control and to establish measures to prevent damage at the time the piping system is designed.

Key points to consider in the design of the pipe system are listed below.

1) The general design of the pipe system should be a loop so that a unidirectional flow supported by suitable devices to prevent backflow may be maintained. The number of bypasses and branches in the system should be minimized.

2) It is recommended that water for injection should be continuously circulated at a temperature of over 80 °C and at a velocity of greater than 1.0 m/sec in order to prevent the growth of microorganisms and the deposit of organic matter. If it is not circulated, the water should be drained and replaced daily.

3) It is desirable that pipelines circulating water at room temperature have UV lamps (germicidal ultraviolet light lamps) mounted intermittently along the course to prevent microbial growth.

4) It is recommended that loop pipelines be equipped with pressure-regulating valves at the end of the loop to ensure a constant flow velocity at all outlets. If valves cannot be installed, loop pipelines should be designed so that there is no backflow from other use points when one is in use.

5) If not continuously circulated within the pipes, water may stagnate and cause contamination. Therefore, documented procedures based on validation results should be established for strict quality control. As a rule, pipes should be flushed with hot water (80°C) every day before use to prevent contamination with microorganisms.

6) Valves connected to branches (e.g., T-shaped pipes) of a loop should be installed as close as possible to the loop to minimize dead legs. As a rule, the distance from the center of the main pipe to the end of the branch should be less than 6 (preferably 3) diameters of the pipe.

7) Pipes should be labeled with the kind of water and the flow direction at suitable intervals for operators' awareness in the area where they may access.

8) Pipes running horizontally should be installed with a gradient of at least 1/100 to prevent the stagnation of water.

9) Pipelines should include adequate water drainage points so that the system may be readily purged. The structure of the pipelines should also be designed to be free from backflow.

10) The installation of a pipeline across processing areas or rooms where cross-contamination poses a serious risk should be avoided; for example, a piping running from an area for a pharmacologically or biologically active product to a general-use area may increase the risk of cross-contamination.

6) Heat Exchangers

Potential contamination of the water supply due to leakage from a heat exchanger should be prevented by using either a double tube-type heat exchanger or a double tube sheet-type heat exchanger. If another type of heat exchanger is used, such as the plate type, potential contamination of the pharmaceutical water due to the heat transfer medium should be prevented by maintaining higher pressure on the pharmaceutical water side. An appropriate device should be installed to monitor the pressure difference.

7) Water Use Points and Sampling Points

In addition to appropriate management procedures, facility and equipment design are also integral to controlling the quality of pharmaceutical water. The following points should be taken into consideration.

1) As a rule, sterilizing filters should not be placed at water use points since the filters could mask microbiological contamination in the water system. Endotoxins could also be released from dead microorganisms retained in the filters. If the use of filters is unavoidable, the interval of replacement should be based on validation results.
2) If it is not possible to sample water from a use point, a sampling port should be installed as close as possible to the use point.
3) Water should be sampled from a use point or sampling port where the sampling procedure can be performed without restrictions. Sampling procedures should be established to avoid an influence from flushing of water nor the sampling containers.
4) Sampling frequency at each sampling point should be specified after examination and consideration of such factors as water quality, consumption, and seasonal variations.

8) Valves and Instruments

Valves, meters, and detectors mounted on water systems should be designed for sanitary applications, e.g., diaphragm types that do not cause water stagnation nor have any dead space. It is recommended that a total organic carbon (TOC) meter (that may also serve as a conductivity meter) be installed in the line in order to monitor the chemical quality of water in a timely manner. The location of probes in the pipes should be at the worst point of water quality.

9) Pumps

Pumps should be designed for sanitary applications, have a sealed casing capable of preventing contamination, and be able to withstand sterilization using hot water or pure steam. Stainless steel centrifugal pumps are generally used. However, it is recommended that the pump total head, discharge capacity, interior contact surface smoothness, and seal integrity be established by taking the following factors in consideration: the largest and smallest consumption of water possible at any one moment; the grade of water quality; and the system configuration, piping system, and predetermined lowest linear velocity of water from the water tank/water distribution piping system to the points of use.

10) Ultraviolet Ray (UV) Lamps for Sterilization and Disinfection

UV lamps may be placed inside water supply pipes for the purposes of disinfection or decomposition of organic matter in water; however, the ability of the UV lamps to disinfect is limited. Utilization of the lamps should be based on good understanding of the principles of UV light disinfection. Points to consider for proper UV lamp installation design are listed below.

1) The recommended UV wavelength for the decomposition of organic matter is 185 nm.
2) The recommended UV wavelength for disinfection is 254 nm. It is important to note that UV lamps have a limited disinfection efficacy at close distance. It should be also noted that efficacy is dependent on temperature, flow velocity, intensity and time of irradiation, and the types of microorganisms targeted. It should also be noted that the typical UV disinfection efficacy is only about 90% at room temperature.
3) For disinfection purposes, a UV lamp should be placed in the circulation loop before the point of use.
4) To decompose the organic matter, water should be pretreated by RO in order to reduce the burden on the UV irradiation. It should be noted that when water is kept circulating for a prolonged period of time while being UV-irradiated, the quality of water will deteriorate due to increased electrical conductivity caused by the decomposition of organic matter.

A2.2 Validation of Pharmaceutical Water

Validation is the verification and documentation of evidence that a specific system, equipment, or process is designed based on a sound scientific rationale and is functioning as intended. Specifically, it is a documented program that provides a high degree of assurance that a system can consistently produce a product which meets predetermined characteristics of quality as expected. Validation defines key process parameters and the scope of operations. The aim of the validation program for facilities, equipment, and systems applicable to pharmaceutical water is to qualify the design of equipment and devices, as well as their installation, operation, and performance. The validation of pharmaceutical water usually consists of several processes, as described below, the most critical of which are determining the appropriate criteria and then evaluating the results obtained against these criteria.

1) Determination of the quality characteristics of pharmaceutical water
2) Determination of an appropriate system for obtaining the desired quality of water from the source water supplied to the purification system
3) Selection of equipment, devices, and process control and monitoring techniques

4) Qualification of equipment and devices designed for pharmaceutical water production [design qualification (DQ)]

5) Installation qualification (IQ)

The following items should be included in IQ.

- Calibration of instruments and devices
- Verification that all equipment and devices are installed according to manufacturers' specifications, that they comply with the approved in-house design, and that the installed water system is operable.

6) Operational qualification (OQ)

The OQ is a procedure for verifying that all equipment and ancillary systems perform as intended throughout the anticipated operating ranges. The OQ includes the following items:

- Tests and checks to verify that the performance of equipment and devices, the alert system, and the control system can be reliably operated
- Tests and checks to verify that alert and action levels are established appropriately

7) Performance qualification (PQ)

Prior to performing the PQ, the critical process parameters must be properly defined, and the equipment and ancillary systems must function effectively and consistently over a sustained period of time. After this has been accomplished, it can be stated that the manufacture of pharmaceutical water is reproducible and conforms to specifications. At this stage of validation, alert and action levels for key characteristics of water quality and process parameters should be established and verified. Usually, the PQ is performed in two steps. During the early stage (phase 1) the consistent production and supply of pharmaceutical water of the required quality is achieved, alert and action levels are established, and SOPs for routine monitoring and control are composed. At the start of qualification, it should be confirmed that all the points for critical processes in the manufacture of water for injection or purified water, the points-of-use in each subloop, are capable of producing and supplying water that complies with predetermined specifications for at least 3 consecutive days to 1 week. Then, in phase 2, follow-up checks should be performed on the same parameters as those established in phase 1 over the course of more than one year. These checks will be done in order to detect any seasonal variations and to confirm the stable operation of the equipment and systems based on relevant documented procedures and control criteria. At the same time, the optimum frequency for changing equipment parts, etc. should be investigated and potential routine monitoring and control problems should be identified. When phase 2 is completed, trend analyses should be

performed with regard to seasonal variations in water quality and to confirm that pharmaceutical water is being consistently produced and is of the required quality. Then, all data and findings should be summarized as a report and the validity of the entire system should be evaluated.

8) Implementation of the "validation maintenance program" (also called the "validation life cycle")

   The validation maintenance program, which consists of the items listed below, should be prepared and implemented.

   - Management of change control for the pharmaceutical water manufacturing system
   - Recalibration
   - Preventative maintenance schedule
   - Monitoring program for critical process parameters
   - Corrective action and preventative action program (CAPA Program)

9) Periodic review of the performance and adequacy of systems (system review)

   A periodic review program should be established. The outcome of the review should provide information that will allow the manufacturer to determine whether these systems are running and functioning in good order.

10) Documentation of the outcome of the above-mentioned steps (1 - 9).

A2.3 Routine Monitoring and Control of Pharmaceutical Water

A2.3.1. Outline

It is essential to perform validation to verify the procedures for routine monitoring and control of pharmaceutical water before starting the routine manufacturing of water. The parameters that are absolutely required for routine monitoring and control include conductivity and total organic carbon (TOC). Parameters to be monitored periodically include these two parameters and, depending on what the water is used for, additional parameters such as the levels or counts of various chemicals, viable microorganisms, endotoxins, particulate matter, etc. The frequency of these measurements should be determined based on how consistently the desired water quality is achieved.

A2.3.2. Sanitization

During validation, it needs to be demonstrated that the sanitization procedures used are capable of reducing the risk of microbial contamination to an allowable level and that the water can be maintained in a contamination-free state. The validation of heat sanitization procedures should include a test to verify that heat is distributed throughout the entire water system. In the case of chemical sanitization, it should be verified that the chemical agent selected can be distributed throughout the entire system at an optimal bactericidal concentration and that the residual chemical agent can be effectively removed by an appropriate means after sanitization.

In general, the frequency of sanitization should be determined based on validation results from the system in question. The frequency of sanitization thus established should be adequate to allow operation of the water system under microbiologically well-controlled conditions, or at least better than the predetermined alert level.

A2.3.3. Sampling

The pharmaceutical water system should be monitored frequently enough to verify that the system is being well controlled and that water of the required quality is being continuously produced. Water samples should be collected from representative points for each process and distribution system. The frequency of sampling should be established according to the validation data, and all critical areas should be included in the validation. The sampling schedule should be also based on the quality of water requested at the planning stage. For example, water sampling will be more frequent for pharmaceutical water than for lower quality water because of stricter microbiological requirements.

It is particularly important to recognize that water sampled from the pharmaceutical water system is representative of the entire system. Sampling ports should be disinfected and flushed with a sufficient amount of water before sampling. Samples containing a disinfectant after disinfection need to be appropriately neutralized prior to microbiological analysis. Samples for microbiological analysis should be tested immediately after sampling or appropriately stored until analysis.

Samples of running water should serve only as an indicator of the concentration of microbes in the pharmaceutical water system. Many microorganisms growing on the inner surfaces of the water tank and water pipes exist as biofilms and are usually present in large amounts. These biofilms then become a source of microorganism colonies floating in the water system. Microorganisms present in biofilms tend to remain a source of contamination from which it is difficult to collect samples or obtain a count. Hence, microorganism colonies are

generally used as an indicator of the level of contamination in the water system and serve as a basis for establishing the alert level for the system. For example, consistently high counts of microorganisms are an indication of increased biofilm growth in the water system, indicating that corrective action should be taken.

A2.3.4. Alarm Levels and Action Levels

The microbial count and other quality-related parameters should be monitored to ensure that the pharmaceutical water system is producing water of an acceptable quality when under continuous operation in accordance with design specification. The monitoring data obtained should be compared with the established process parameter limits or specifications for purified water, in-process products, or final products. In addition, appropriate alert and action levels should be set separately (based on the reference information contained in the General Tests, Processes, and Apparatus section of the Japanese Pharmacopoeia) and used for process control rather than for the determination of acceptance criteria.

Definition of "Alert" Levels

If the presence of microbes reaches the alert level, it indicates a possible deviation from normal operation and process parameter values. The alert level serves as a warning, but corrective actions do not necessarily have to be taken.

Definition of "Action" Levels

Action levels are an indicator of actual deviations from normal operations when process parameter values exceed the specified limits. Corrective actions to restore the normal operation should be taken immediately by identifying the causes of the deviations.

A2.3.5. Microbiological Monitoring

The primary purpose of the microbiological monitoring program for the pharmaceutical water system is to predict the deterioration of the microbiological quality of water and to prevent the deterioration from having an impact on the quality of the final pharmaceutical water product. The microbiological quality of the water can be maintained at an appropriate level by conducting a trend analysis of the microbiological data collected as well as by the control of specific microorganisms that need to be eliminated from the system. It is not necessary to detect all types of microorganisms present in the water system; however, the monitoring program

should be capable of detecting a wide range of the microorganisms that could be present, including those that grow slowly.

The microbiological limits for pharmaceutical water should be appropriately established by referring to the limits specified in the General Tests, Processes, and Apparatus section of the Japanese Pharmacopoeia. If a microbial count exceeds the specified action level during validation or routine monitoring, the properties of the bacterial isolates should be examined. When many objectionable aquatic microorganisms are detected in large quantities, the possible existence of biofilms in the water system should be suspected and appropriate sterilization and sanitization should be performed to decontaminate the system.

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

Action and alert levels for conductivity and TOC should conform to accepted microbiological limits. If the measured values of these parameters exceed alert levels, monitoring frequency should be increased and other measures taken to determine the causes of the abnormalities. If the measured values of these parameters exceed action levels, access to the water system should be suspended, measures should be taken to determine the causes of the deviation, and the system malfunction(s) should be corrected. Appropriate corrective measures should then be taken to assure consistent water quality that meets the specified conductivity and TOC limits.

Whenever water quality is monitored and controlled by conductivity and TOC testing, it is not usually necessary to monitor individual metals or inorganic ions. However, the information provided by these parameters is useful when measured values exceed the action or alert levels.

A2.4 Training of Personnel Engaged in Pharmaceutical Water Production

Appropriate education and training on the production and quality control of pharmaceutical water should be provided for personnel who engage in the operation and maintenance of the facility and equipment as well as water quality testing in order to produce pharmaceutical water of the required quality.

The training program should include, but not be limited to, the following:

1) The correlation between the quality of pharmaceutical water to be used for the manufacture of each class of drug products