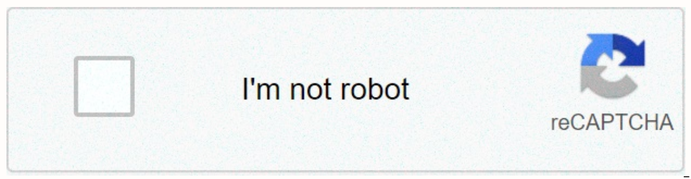

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Purified water bp monograph pdf

» Purified water is water obtained by an appropriate process. It is prepared from compliance with water with the U.S. National Environmental Protection Agency or the USP29 drinking water regulations of the European Union, Japan or the World Health Organization Guidelines for Drinking Water Quality. Contains no added substance. NOTE — Purified water is intended to be used as an ingredient in official preparations and in tests and tests, unless otherwise specified (see Water in Ingredients and Processes and in Tests and Tests under General Warnings and Requirements). When used for sterile dosage forms, except for parenteral administration, process the article to meet the requirements in Sterility Tests 71, or first make Purified Water sterile and then protect it from microbial contamination. Do not use purified water in preparations intended for parenteral administration. For such purposes, use injection water, bacteriostatic water for injection, or sterile water for injection. Tests for total organic carbon and conductivity apply to Purified Water produced on site for use as an ingredient in official preparations and in tests and tests. Purified water packed in bulk for commercial use elsewhere meets the requirements of all tests in Sterile Purified Water, except Labeling and Sterility 71. 1231 WATER FOR PHARMACEUTICAL PURPOSES Water is widely used as raw material, ingredient and solvent in the processing, formulation and manufacture of pharmaceuticals, active pharmaceutical ingredients (APIs) and intermediates, compendial articles and analytical reagents. This general information chapter provides additional information about water, its quality attributes that are not included in a water monograph, processing techniques that can be used to improve water quality, and a description of the minimum water quality standards that should be considered when selecting a water source. This information chapter is not intended to replace existing regulations or guides that already exist to cover U.S. and International GMP issues (ICH or WHO), engineering guides, or other regulatory guidelines (FDA, EPA, or WHO) for water. The contents will help users better understand pharmaceutical water issues and some of the microbiological and chemical concerns unique to water. This chapter is not an inclusive writing on pharmaceutical waters. Contains points that are basic information to be considered, when appropriate, for the processing, retention and use of water. It is the user's responsibility to ensure that pharmaceutical water and its production comply with applicable government regulations, guidelines and compendial specifications for the types of water used in compendial articles. The control of the chemical purity of these waters is important and is the main purpose of the monographs in this compendium. To other official articles, bulk water monographs (Purified (Purified and Injection Water) also limit how the article can be produced by believing that the nature and robustness of the purification process is directly related to the resulting purity. The chemical attributes listed in these monographs should be considered as a set of minimum specifications. Stricter specifications may be required for some applications to ensure suitability for specific uses. The basic guidance on the proper applications of these waters is found in the monographs and is further explained in this chapter. Microbiological water quality control is important for many of its uses. All forms of packaged water that have monograph patterns are required to be sterile because some of their intended uses require this attribute for health and safety reasons. USP determined that a microbial specification for bulk monograph waters is inadequate and was not included in the monographs for these waters. These waters can be used in a variety of applications, some requiring extreme microbiological control and others requiring none. The microbial specification required for a given bulk water depends on its use. A single specification for this difficult-to-control attribute would unnecessarily overload some water users with irrelevant specifications and tests. However, some applications may require even more careful microbial control to prevent the proliferation of microorganisms ubiquitous to water during the purification, storage and distribution of this substance. A microbial specification would also be inadequate when related to the usefulness or continuous nature of supplyof this raw material. Microbial specifications are typically evaluated by test methods that take at least 48 to 72 hours to generate results. Because pharmaceutical waters are generally produced by continuous processes and used in products and manufacturing processes soon after generation, it is likely that the water was used well before the definitive test results were available. Failure to comply with a compendial specification would require investigating the impact and making an approval/failure decision on all product batches between the acceptable test result of the previous sampling and the acceptable result of a subsequent sampling. The technical and logistical problems created by a delay in the result of such analysis do not eliminate the user's need for microbial specifications. Therefore, these water systems need to be operated and maintained in a controlled manner, which requires that the system be validated to ensure operational stability and that its microbial attributes be monitored quantitatively against established alert and action levels that provide an early indication of system control. Water system validation issues and alert/action levels and specifications included in this chapter. WATER OR FEED CONSIDERATIONS To ensure compliance with certain minimum standards of chemical and microbiological, microbiological, quality, used in the production of medicinal substances or as a source or feed water for the preparation of the various types of purified water must meet the requirements of the National Primary Drinking Water Regulation (NPDWR) (40 CFR 141) issued by the U.S. Environmental Protection Agency (EPA) or the drinking water regulations of the European Union or Japan, or who's drinking water guidelines. The limits of the types and quantities of certain organic and inorganic contaminants ensure that water will contain only small safe amounts of potentially objectionable chemical species. Therefore, water pretreatment systems will only be challenged to remove small amounts of these potentially difficult chemicals to remove. In addition, the control of objectionable chemical contaminants in the source water stage eliminates the need to specifically test some of them (e.g., trihalometanos and heavy metals) after the water has been purified. The microbiological requirements of drinking water ensure the absence of coliforms, which, if determined as of fecal origin, may indicate the potential presence of other potentially pathogenic microorganisms and viruses of fecal origin. Compliance with these microbiological requirements does not exclude the presence of other microorganisms, which could be considered undesirable if found in a medicinal substance or formulated product. To perform microbial control, municipal water authorities add disinfectants to drinking water. Oxidizing and chlorine-containing substances have been used for many decades to this end and have generally been considered relatively harmless to humans. However, these oxidants may interact with naturally occurring organic matter to produce disinfection by-products (DBPs), such as trihalomethanes (THMs, including chloroform, bromodchloromethane and dibromochloromethane) and haloacetic acids (HAAs, including dichlorocaric acid and trichloroacetic acid). The levels of DBPs produced vary according to the level and type of disinfectant used and the levels and types of organic materials found in water, which may vary seasonally. Because high levels of DBPs are considered a health risk in drinking water, the Drinking Water Regulation determines their control at generally accepted nonhazardous levels. However, depending on the unit operations used for water purification, a small fraction of the DBPs in the initial water can lead to finished water. Therefore, it is important to have minimum levels of DBPs in the initial water, while achieving an effective disinfection. BPD levels in drinking water can be minimized by using disinfectants such as ozone, chloromines or chlorine dioxide. Like chlorine, its oxidative properties are sufficient to damage some operations of the pretreatment unit and should be removed at the beginning of the pre-treatment. Complete removal of some of these disinfectants can be problematic. For example, chloromines may degrade during disinfection disinfection or during the removal of the pretreatment, thus releasing ammonia, which in turn can lead to the finished water. The operations of the pretreatment unit shall be designed and operated to adequately remove disinfectant, drinking water and objectionable disinfectant DBPs. A serious problem could occur if the unit's operations designed to remove chlorine were, without warning, challenged with chlorine-containing drinking water from a municipality that had been forced to cease the use of chlorine disinfection to comply with the EPA's drinking water THM specifications. The dechlorination process can completely remove chloromine, which could irreparably damage the operations of the downstream unit, but also the release of ammonia during this process can lead through pretreatment and prevent the finished water from passing the compendial conductivity specifications. The purification process should be reevaluated if the drinking water disinfectant is changed, emphasizing the need for a good working relationship between the pharmaceutical water manufacturer and the drinking water supplier. There are many different degrees of water used for pharmaceutical purposes. Several are described in USP monographs that specify uses, acceptable methods of preparation, and quality attributes. These waters can be divided into two general types: bulk waters, which are typically produced at the place where they are used; and packaged waters, which are produced, packed and sterilized to preserve microbial quality throughout their packaged service life. There are several specialized types of packaged water, differing in their designated applications, packaging limitations and other quality attributes. There are also other types of water for which there are no monographs. They are bulk waters, with names given for descriptive purposes only. Many of these waters are used in specific analytical methods. The associated text cannot specify or imply certain quality attributes or preparation modes. Such uncoordinated waters may not necessarily adhere strictly to the preparation modes or attributes indicated or implicit. Water produced by other means or controlled by other test attributes may also satisfy the intended uses for those waters. It is the user's responsibility to ensure that such waters, even if produced and controlled exactly as indicated, are suitable for the intended use. Wherever the term water is used within this compendia without other adjectives or descriptive clauses, the intention is that water of no less purity than purified water is used. The following is a brief description of the various types of pharmaceutical waters and their significant uses or attributes. Figure 1 can also be useful for understanding some of the various types of water. Fig. 1. Water for pharmaceutical purposes. Bulk monograph and steam waters The following waters are typically produced in volume by a water system operating several units and distributed by a pipe piping system use on the same site. These specific pharmaceutical waters must meet the quality attributes specified in the related monographs. Purified Water — Purified Water (see USP monograph) is used as an excipient in the production of non-parenteral preparations and in other pharmaceutical applications, such as cleaning of certain equipment and non-contact non-parenteral product-contact components. Unless otherwise specified, Purified Water should also be used for all tests and tests for which water is indicated (see General Notices and Requirements). Purified Water is also referenced throughout USP-NF. Regardless of the font and the box of letters used in its spelling, the water that conforms to the purified water monograph is intended. Purified water must meet the requirements for ionic and organic chemical purity and must be protected against microbial contamination. The minimum quality of the source or feed water for the production of Purified Water is Drinking Water. This source water can be purified through unit ary operations that include deionization, distillation, ion exchange, reverse osmosis, filtration or other appropriate purification procedures. Purified water systems must be validated to reliably and consistently produce and distribute water of acceptable chemical and microbiological quality. Purified water systems that operate under environmental conditions are particularly susceptible to the establishment of tenacious biofilms of microorganisms, which may be the source of undesirable levels of viable microorganisms or endotoxins in the effluent water. These systems require frequent hygiene and microbiological monitoring to ensure adequate microbiological quality water at the points of use. The purified water monograph also allows bulk packaging for commercial use elsewhere. When this is done, the necessary specifications are those of the water packed Sterile Purified Water, except sterility and labeling. There is a potential for microbial contamination and other quality changes of this non-sterile bulk packed water. Therefore, this form of Purified Water should be prepared and stored in such a way that it limits microbial growth and/or simply used in a timely manner before microbial proliferation makes it unsuitable for its intended use. Also depending on the material used for packaging, there may be extractable compounds leaching into the packaging water. Although this article may meet its necessary chemical attributes, such extractables can make water an inappropriate choice for some applications. It is the user's responsibility to ensure the fitness for use of this packaged item when used in manufacturing, clinical or analytical applications where the pure bulk form of water is indicated. Water for Injection — Injection water (see USP monograph) is used as an excipient in the production of parenteral and other preparations where the endotoxin content of the product should be controlled, and in other pharmaceutical applications, such as cleaning of certain equipment and parenteral components of product contact. The minimum quality of supply or feed water for injection water generation is drinking water defined by the EPA of the US, EU, Japan or WHO. This source water can be pretreated to make it suitable for subsequent distillation (or any other validated process is used according to the monograph). The finished water must meet all chemical requirements for purified water, as well as an additional specification of bacterial endotoxin. Since endotoxins are produced by the types of microorganisms prone to inhabiting water, the equipment and procedures used by the system to purify, store and distribute water for injection should be designed to minimize or prevent microbial contamination, as well as remove the incoming endotoxin from the initial water. Injection water systems must be validated to reliably and consistently produce and distribute this water quality. The Water for Injection monograph also allows it to be packed in bulk for commercial use. The necessary specifications include testing for bacterial endotoxins, and those of the water packed Sterile Purified Water, except for Labeling. Bulk packed water for injection is required to be sterile, thus eliminating changes in the quality of microbial contamination. However, packaging extractables can make this water an inappropriate choice for some applications. It is the user's responsibility to ensure the fitness for use of this packaged item when used in manufacturing, clinical or analytical applications where the purest bulk form of water is indicated. Water for Hemodialysis — Hemodialysis water (see usp monograph) is used for hemodialysis applications, especially the dilution of concentrated hemodialysis solutions. It is produced and used on site and is made of EPA drinking water that has been purified to reduce chemical and microbiological components. It can be packed and stored in non-reactive containers that prevent bacterial entry. The term non-reactive containers imply that the container, especially its water contact surfaces, are not altered in any way by water, such as by leaching of compounds related to the container in water or by any chemical reaction or corrosion caused by water. Water does not contain added antimicrobials and is not intended for injection. Its attributes include specifications for water conductivity, total organic carbon (or oxidized substances), microbial limits, and bacterial endotoxins. Water conductivity and total organic carbon attributes are identical to those established for purified water and water for injection; however, instead of total organic carbon, organic content can be measured alternatively by testing oxidized substances. The attribute of microbial limits for this water is unique among the monographs of water to but is justified on the basis of the specific application of that water that has microbial microbial content related to its safe use. The attribute bacterial endotoxins is also established at a level related to their safe use. Pure Steam — Pure Steam is intended to be used in porous steam sterilization loads and equipment and other processes, such as cleaning where condensate would contact directly with official items, containers for these articles, process surfaces that, in turn, would come into contact with these articles or materials that are used in the analysis of these articles. Pure Steam can be used for air humidification in controlled manufacturing areas where official items or article contact surfaces are exposed to the resulting air conditioner. The primary intention of using this quality of steam is to ensure that official articles or article contact surfaces exposed to it are not contaminated by waste within the steam. Pure Steam is prepared from properly pretreated source water, analogous to pretreatment used for purified water or injection water, vaporized with adequate mist elimination, and distributed under pressure. Sources of undesirable contaminants within Pure Steam may be derived from water droplets from an inlet source, anti-corrosion vapor additives, or particulate matter from the steam production and distribution system itself; therefore, the attributes in the monograph should prevent most contaminants that could arise from these sources. These attributes of purity are measured in the condensed of the article, and not in the article itself. This, of course, gives great importance to the cleaning of the process of generation and collection of pure vapor condensates, as it should not negatively impact the quality of the resulting condensed fluid. Other steam attributes not detailed in the monograph, in particular the presence of even small amounts of unrecognizable gases or the existence of an overheated or dry state, may also be important for applications such as sterilization. The large release of energy (latent condensation heat) as water changes from the gaseous state to the liquid is the key to the effectiveness of steam sterilization and its efficiency, in general, as a heat transfer agent. If this phase change (condensation) is not allowed because the steam is extremely hot and in a persistent state super heated and dry, then its usefulness can be seriously compromised. Non-condensable gases in steam tend to stratify or collect in certain areas of a steam sterilization chamber or its load. These surfaces would therefore be at least partially isolated from the phenomenon of vapor condensation, preventing them from experiencing all the energy of the sterilizing conditions. Therefore, controlling these types of steam attributes, in addition to their chemical purity, can also be important for certain Pure Steam applications. However, because these additional attributes are usage-specific, they are not in the Pure Steam monograph. Note that less pure vegetable steam can be used for steam sterilization of non-poraly loads, general general and

sterilization of non-product contact equipment and analytical materials, air humidification in non-manufacturing areas, where used as a non-product contact heat exchange medium, and in all compatible applications involved in the manufacture of chemicals and bulk API. Packaged monographed waters The following monograph waters are packed forms of purified water or injection water that have been sterilized to preserve their microbiological properties. These waters may have specific uses as indicated by their names, and may also have restrictions on packaging settings related to those uses. In general, these packed waters can be used instead of the bulk form of water from which they were derived. However, the user should take into account that the packaging and sterilization processes used for the articles can remove materials from the packaging material into the water during their useful life, making it less pure than the original water placed on the packaging. The chemical attributes of these waters are still defined mainly by wet chemistry methods and specifications similar to those previously used for bulk pharmaceutical waters before their replacement by water conductivity and total organic carbon (OCD). It is the user's responsibility to ensure the fitness for use of this article when used in manufacturing, clinical or analytical applications where the purest bulk form of water is indicated. Sterile Purified Water — Sterile Purified Water (see USP monograph) is purified, packaged, and sterile water. It is used in the preparation of non-parenteral compendial dosage forms or in analytical applications requiring purified water where access to a validated purified water system is not practical, where only a relatively small amount is required, where sterile purified water is required, or where bulk packed purified water is not adequately controlled microbiologically. Sterile injection water — Sterile injection water (see USP monograph) is packaged and sterile injection water. It is used for extimeraneous prescription compounds and as sterile diluent for parenteral products. It can also be used for other applications where bulk water for injection or purified water is indicated, but when a validated water system is evaluated or not practical or where only a relatively small amount is required. Sterile injection water is packed in single-dose containers not larger than 1 L in size. Bacteriostatic water for injection — Bacteriostatic water for injection (see usp monograph) is sterile injection water, to which one or more suitable antimicrobial preservatives have been added. It is intended to be used as diluted in the preparation of parenteral products, most typically for multi-dose products that require repeated removals of content. Can be packed in single-dose or multi-dose containers not exceeding 30 mL. Sterile water for irrigation- irrigation- Water for Irrigation (see USP monograph) is water for injection packed and sterilized in single-dose containers larger than 1 L size that allows the rapid delivery of its contents. It does not need to meet the requirement under small volume injections in the general particulate matter test chapter in 788 injections. It can also be used in other applications, which do not have particulate material specifications, where bulk water for injection or purified water is indicated, but where access to a validated water system is not practical or where slightly larger quantities than are supplied as sterile water for injection are required. Sterile Inhalation Water — Sterile Inhalation Water (see USP monograph) is injection water that is packed and made sterile and intended for use in inhalers and in the preparation of inhalation solutions. It carries a less stringent specification for bacterial endotoxins than Sterile Water for Injection and is therefore not suitable for parenteral applications. Non-monographed manufacturing waters In addition to the bulk monograph waters described above, non-monographed waters can also be used in pharmaceutical processing steps such as cleaning, synthetic steps, or as starter material for further purification. The following is a description of several of these unphotographed waters, as mentioned in various locations within this compendia. Drinking water — This type of water may be referred to as Drinking Water (meaning drinking or drinking able), national primary drinking water, primary drinking water, or national drinking water. Except when a unique drinking water specification is declared (such as the NPDWR [U.S. Environmental Protection Agency National Drinking Water Regulation, as cited in 40 CFR Part 141]), that water must comply with npdwr quality attributes, or the Drinking Water Regulations of the European Union or Japan, or the WHO Drinking Water Guidelines. It can be derived from a variety of sources, including a public water utility, a private water supply (e.g. a well), or a combination of those sources. Drinking water can be used in the early stages of cleaning pharmaceutical manufacturing equipment and product contact components. Drinking water is also the minimum quality of water that should be used for the preparation of official substances and other pharmaceutical ingredients in bulk. When compatible with the processes, the levels of contaminants allowed in Drinking Water are generally considered safe for use for official substances and other medicinal substances. When required by the processing of materials to achieve their required final purity, higher water qualities may be required for these manufacturing steps, perhaps even as pure as injection water or purified water. Such higher purity waters, however, may require only purity than Drinking Water (see Figure 2 below). Drinking water is the prescribed source or feeding water production of pharmaceutical waters bulk monographs. The use of the Drinking Water specifications establishes a reasonable set of maximum permitted levels of chemical and microbiological contaminants with which a water purification system will be challenged. As seasonal variations in the quality attributes of the drinking water supply may occur, its synthetic and cleaning uses should be considered. Processing steps in pharmaceutical water production should be designed to accommodate this variability. Fig. 2. Selection of water for pharmaceutical purposes. Hot Purified Water - This water is used in usp-nf's article preparation instructions and is clearly intended to be purified water that has been heated to an unspecified temperature in order to improve solubilization of other ingredients. There is no upper temperature limit for water (other than being less than 100), but for each monograph there is an implicit lower limit below which the desired solubilization effect would not occur. Non-monographed Analytical Waters Both general warnings and requirements and the introductory section of Reagents, Indicators and Solutions clearly state that when the term water, without qualification or other specification, is indicated for use in analyses, the water quality will be purified water. However, there are numerous qualifications. Some of these qualifications involve preparation methods, from specifying the primary purification step to specifying additional purification. Other qualifications require that specific attributes be fulfilled that can interfere with analytical processes. In most of these latter cases, the required attribute is not specifically tested. Instead, a new purification process is specified that ostensibly allows water to adequately meet this required attribute. However, the preparation instructions for many reagents were taken from the innovator's laboratories to the monograph originally introduced for a particular USP-NF article or general test chapter. The water quality of the reagent described in these tests may reflect the designation of the water quality of the innovator's laboratory. These specific water designations may have originated without the innovator's awareness of the requirement for purified water in USP-NF tests. Regardless of the original reason for the creation of these numerous special analytical waters, it is possible that the attributes of these special waters can now be fulfilled by the basic stages of preparation and current specifications of Purified Water. In some cases, however, some of the post-processing steps cited are still necessary to reliably achieve the necessary attributes. Users are not required to employ specific and perhaps archaicly generated forms of analytical water where there may be alternatives with equal or better quality, availability or performance Consistency and reliability to produce these alternative alternatives the waters should be checked as producing the desired attributes. In addition, any alternative analytical water should be evaluated per application per application by the user to ensure its suitability. The following is a summary of the various types of non-monographed analytical waters that are mentioned in USP-NF. Distilled Water — This water is produced by vaporizing liquid water and condensing it into a purer state. It is mainly used as a solvent for reagent preparation, but is also specified in the execution of other aspects of the tests, such as to rinse an analyt, transfer a test material such as slurry, as calibration standard or analytical white, and for cleaning test devices. It is also cited as the initial water to be used for the manufacture of high purity water. Since none of the aforementioned uses of this water implies the need for a particular purity attribute that can only be derived by distillation, water that meets the requirements of Purified Water derived by other means of purification could be equally adequate when distilled water is specified. Freshly distilled water — Also called freshly distilled water, it is produced in a similar way to Distilled Water and should be used soon after its generation. This implies the need to avoid contamination by endotoxins, as well as any other adventurous forms of air contamination or containers that may arise with prolonged storage. It is used to prepare solutions for subcutaneous animal test injections as well as for a reagent solvent in tests for which there appears to be no particularly high water purity required that could be attributable to being freshly distilled. In test-animal use, the term newly distilled and its use of tests imply a chemical, endotoxin and microbiological purity that could be equally satisfied by Water for Injection (although no reference is made to these chemical, endotoxin or microbial attributes or specific protection against recontamination). For non-animal uses, water that throws the requirements for purified water derived by other purification means and/or storage periods may be equally suitable when freshly distilled water or freshly distilled water is specified. Deionized water — This water is produced by an ion exchange process in which contamination ions are replaced by H+ or OH ions. Like Distilled Water, Deionized Water is primarily used as a solvent for reagent preparation, but is also specified in the execution of other aspects of testing, such as the transfer of an analysis within a test procedure, as a calibration standard or in analytical blank, and for cleaning test devices. Moreover, none of the aforementioned uses of this water implies any attribute of necessary purity that can only be achieved by deionization. Therefore, water that atthe requirements for purified water derived from other means of could also be adequate when deionized water is specified. Newly deionized water - This water is prepared in a Fashion for Deionized Water, although as the name suggests, it should be used soon after its production. This implies the need to avoid any adventurous contamination that may occur in storage. This water is indicated for use as a reagent solvent as well as for cleaning. Due to the nature of the tests, Purified Water may be a reasonable alternative to these applications. Deionized Distilled Water - This water is produced by decoupled decoupled water (see Deionized Water). This water is used as a reagent in a liquid chromatography test that requires a high purity. Due to the importance of this high purity, water that barely meets the requirements for purified water may not be acceptable. High purity water (see below) may be a reasonable alternative to this water. Distilled or deionized filtered water — This water is essentially purified water produced by distillation or deionization that has been filtered through a membrane rated at 1.2-µm. This water is used in particulate material tests where the presence of particles in water could influence the test results (see Particulate Matter in Injections 788). As the chemical purity of the water required for this test could also be provided by water purification processes other than distillation or deionization, the water filtered meeting the requirements of Purified Water, but produced by different means of distillation or deionization could be equally adequate. Filtered Water — This water is purified water that has been filtered to remove particles that could interfere with the analysis where water is used. When used to prepare samples for particulate matter testing (see Particulate Matter in injections 788), although not specified in monographs, water filtration should be through a 1.2-µm filter to be consistent with the general chapter of testing. When used as a chromatography reagent, the filter classifications specified by the monograph range from 0.5 µm to unspecified. High Purity Water — The preparation of this water is defined in Containers 661. It is water that is prepared by deionizing the previously distilled water and then filtering it through a nominal membrane of 0.45-µm. This water must have an inline conductivity of not more than 0.15 µS/cm (6.67 Megohm-cm) to 25. For purity comparison, the analogous requirements of stage 1 and 2 conductivity for purified water at the same temperature are 1.3 µS/cm and 2.1 µS/cm, respectively. The preparation specified in Containers 661 uses materials that are highly efficient deionizers and that do not contribute copper or organic ions to water, ensuring high quality water. If water of this purity comes into contact with the atmosphere even if it is being used or removed from its purification system, its conductivity will immediately degrade, at about 1.0 µS/cm, as atmospheric carbon dioxide dissolves water and balances to bicarbonate ions. Therefore, if analytical use requires that the purity of water remains as high as possible, its use protected from atmospheric exposure. This water is used as a reagent, as a solvent for the preparation of reagents, and for cleaning test devices where less pure waters would not function in an acceptable manner. However, if the user's routinely available purified water is filtered and meets or exceeds the conductivity specifications of High Purity Water, it can be used instead of High Purity Water. Ammonia-free water — Functionally, this water should have an insignificant ammonia concentration to avoid interference in ammonia-sensitive tests. It has been equated with high purity water that has a significantly tighter stage 1 conductivity specification than purified water due to the latter's allowance for a minimum level of ammonium among other ions. However, if the user's purified water were filtered and met or exceeded the conductivity specifications of High Purity Water, it would contain insignificant ammonia or other ions and could be used instead of High Purity Water. Carbon dioxide-free water — The introductory part of the Reagents, Indicators, and Solutions section defines this water as purified water that has been vigorously boiled for at least 5 minutes, then cooled and protected from atmospheric carbon dioxide absorption. Because carbon dioxide absorption tends to reduce water pH, most uses of water without carbon dioxide are associated as solvent in pH or pH-related determinations or as solvent in carbonate-sensitive reagents or determinations. Another use of this water is for certain optical rotation and color and clarity of solution tests. Although it is possible that this water is indicated for these tests simply because of its purity, it is also possible that the pH effects of carbon dioxide containing water may interfere with the results of these tests. A third plausible reason for this water to be indicated is that degassing air bubbles can interfere with these photometric tests. The boiled water preparation approach will also considerably reduce the concentrations of many other dissolved gases, along with carbon dioxide. Therefore, in some of the applications for water without carbon dioxide, it may be the inadvertent desalination effect that actually makes this water adequate. In addition to boiling, deionization is perhaps an even more efficient process to remove dissolved carbon dioxide (drawing the dissolved gas balance toward the ionized state with subsequent removal by ion exchange resins). If the initial purified water is prepared by an efficient deionization process and protected after deionization of atmospheric air exposure, carbon dioxide-free water can be effectively made without the application of heat. However, this process of deionization does not desaera the water, therefore, if the purified water prepared by deionization is considered as a substitute in a test that requires water without carbon dioxide, the user should check if it is not really water similar to Deaerrated Deaerrated (discussed below) that is required for testing. As indicated in High Purity Water, even a brief contact with the atmosphere can allow small amounts of carbon dioxide to dissolve, ionize and significantly degrade conductivity and reduce pH. If analytical use requires that water remains as pH neutral and as carbon dioxide-free as possible, even analysis should be protected from atmospheric exposure. However, in most applications, atmospheric exposure during testing does not significantly affect its suitability in the test. Ammonia-free water and carbon dioxide - As implied by the name, this water should be prepared by approaches compatible with those mentioned for both ammonia-free water and water without carbon dioxide. Because the carbon dioxide-free attribute requires post-production protection from the atmosphere, it is appropriate to first make water ammonia-free using the high purity water process followed by the boiling and carbon dioxide protected cooling process. The process of deionizing high purity water for the creation of ammonia-free water will also remove the ions generated from dissolved carbon dioxide and, finally, by forced equilibrium to the ionized state, all dissolved carbon dioxide. Therefore, depending on its use, an acceptable procedure for the manufacture of ammonia and carbon dioxide free water could be to transfer and collect high purity water in a container protected by carbon dioxide intrusion. Deaeared water — This water is purified water that has been treated to reduce the dissolved air content by appropriate means. In the Reagents section, approaches to boiling, cooling (similar to water without carbon dioxide, but without atmospheric protection of carbon dioxide), and sonication are given as applicable for test uses other than drug dissolution and release tests. Although deaerated water is not mentioned by name in Dissolution 711, suggested methods for deaeration dissolving media (which may be water) include heating to 41, vacuum filtering through a membrane rated at 0.45-µm, and vigorously shaking the filtrate while maintaining vacuum. This chapter specifically indicates that other validated approaches can be used. In other monographs that also do not mention deaerate water by name, the degassing of water and other reagents is performed by means of sparging with helium. Desalination water is used both in dissolution tests and in liquid chromatography applications where outgassing can interfere with the analysis itself or cause erroneous results due to inaccurate bulky withdrawals. Applications where ambient temperature water is used for the preparation of reagents, but tests are carried out at high temperatures, are candidates for outgassing purposes. Whether outgassing could interfere with test performance, including, flow colorimetric or photometric measurements, or volumetric accuracy, so deaenada water should probably be used, whether in the analysis or not. The above above approaches may not make water gas-free. At best, they reduce dissolved gas concentrations so that the gases caused by temperature changes are not likely. Freshly boiled water — This water may include freshly boiled or freshly boiled water (with or without mention of cooling in the heading), but cooling before use is clearly intended. Occasionally it is necessary to use when it is hot. Recently, boiled water is specified because it is used in a pH-related test or carbonate-sensitive reagent, in an oxygen-sensitive test or reagent, or in a test where outgassing could interfere with the analysis, such as specific gravity or an appearance test. Water without oxygen — The preparation of this water is not specifically described in compendia. There is also no oxygen specification or analysis mentioned. However, all uses involve analyses of materials that may be sensitive to oxidation by atmospheric oxygen. Procedures for the removal of dissolved oxygen from solvents, although not necessarily water, are mentioned in Polarography 801 and Spectrophotometry and Light Scattering 851. These procedures involve the simple distribution of the liquid with an inert gas, such as nitrogen or helium, followed by inert gas coverage to avoid oxygen resorption. The cited sparging times range from 5 to 15 minutes to an unspecified period. Some purified water and water injection systems produce water that is kept in a warm state and which is covered inert gas during its preparation and storage and distribution. Although oxygen is poorly soluble in hot water, this water may not be oxygen-free. Any procedure used for oxygen removal should be checked as a reliable production water and suitable for use. LAL reagent water — This water is also referred to as endotoxin-free water. This is usually injection water, which may have been sterilized. It is free of an endotoxin level that would produce any detectable reaction or interference with the limulus amebocyto lysate reagent used in bacterial endotoxin test 85. Water without organic — This water is defined by Organic Volatile Impurities 467 as not producing significantly interfering gas chromatography spikes. The referenced monographs specify the use of this water as a solvent for standard preparation and test solution for testing organic volatile impurities — This water is used as a transfer diluent for an analyt in a Lead 251 test. Although no specific instructions are given for its preparation, it should not contain any detectable lead. Purified water should be a suitable substitute for this water. Chloride-free water — This water is specified as solvent for use in a test that contains a reagent that precipitates in the presence of chloride. Although no specific instructions are given for for this water, its quite obvious attribute is to have a very low chloride level in order not to be active with this chloride-sensitive reagent. Purified water could be used for this water, but it should tested to ensure that it is not active. Hot Water — The uses of this water include solvents to achieve or improve the solubilization of the reagent, restore the original volume of cooked or hot solutions, rinse insoluble analyts free of impurities soluble in hot water, solvents for recrising reagent, cleaning of appliances and as a solubility attribute for various USP-NF articles. In only one monograph is the specified hot water temperature; Thus, in all other cases, the water temperature is less important, but should be high enough to achieve the desirable effect. In all cases, the chemical quality of water is implied as that of Purified Water. VALIDATION AND QUALIFICATION OF WATER PURIFICATION, STORAGE AND DISTRIBUTION SYSTEMS Establishing the reliability of pharmaceutical water purification, storage and distribution systems requires an appropriate period of monitoring and observation. Usually, few problems are found in maintaining the chemical purity of purified water and water for injection However, the advent of the use of conductivity and OCD to define chemical purity allowed the user to evaluate more quantitatively the chemical purity of water and its variability due to the maintenance and regeneration of the routine pretreatment system. Even the presence of such unit operations as heat exchangers and point-of-use hoses can compromise the chemical quality of the water inside and delivered from a well-controlled water system. Therefore, an assessment of the consistency of the chemical purity of water over time should be part of the validation program. However, even with the best controlled chemical quality, it is often more difficult to consistently meet the microbiological quality criteria established due to the phenomena that occur during and after chemical purification. A typical program involves intensive daily sampling and testing of important process points for at least one month after creating operational criteria for each unit operation, point of use, and sampling point. A neglected aspect of water system validation is the delivery of water to its actual location of use. If this process of transferring the outlets from the distribution system to the water use sites (usually with hoses) is defined as outside the water system, then this transfer process still needs to be validated so as not to negatively affect water quality as it becomes unfit for use. Because routine microbial monitoring is performed for the same transfer process and components (e.g., hoses and heat exchangers) as routine water use (see Sample considerations), there is some logic to include this water transfer process within the validation of the distribution system. Validation is the process by which proofing at a high level of ensuring that a specific process will consistently produce a product in accordance with an established set of quality attributes is acquired and documented. Before and during the beginning critical process parameters and their operational ranges are established. A validation program qualifies and documents the design, installation, operation and performance of the equipment. It starts when the system is defined and goes through several stages: installation qualification (IQ), operational qualification (QE), and performance qualification (PQ). A graphical representation of a typical water system validation lifecycle is shown in Figure 3. Fig. 3. Water system validation life cycle. A validation plan for a water system typically includes the following steps: (1) establishing standards for quality attributes of finished water and spring water; (2) define the appropriate operations of the unit and its operational parameters to achieve the desired finished water quality attributes from the available source water; (3) select piping technologies, equipment, controls and monitoring; (4) develop an IQ stage composed of instrument calibrations, inspections to verify that the drawings accurately portray the final configuration of the water system and, when necessary, special tests to verify that the installation meets the design requirements; (5) develop a QM stage composed of tests and inspections to verify that equipment, system alerts and controls are operating reliably and that appropriate alert and action levels are established (This qualification phase may overlap with aspects of the next step.); and (6) develop a prospective pq step to confirm the adequacy of operational ranges of critical process parameters (During this validation phase, alert and action levels are verified for key quality attributes and operational parameters.); (7) ensure the adequacy of ongoing control procedures, e.g. the frequency of hygiene; (8) complement a validation maintenance program (also called a continuous validation lifecycle) that includes a water system change control mechanism and establishes and performs scheduled preventive maintenance, including instrument recalibration (In addition, validation maintenance includes a monitoring program for critical process parameters and a corrective action program.); (9) establish a schedule for periodic review of system performance and requalification, and (10) complete protocols and document Steps 1 to 9. PURIFIED WATER AND WATER FOR INJECTION SYSTEMS The design, installation and operation of purified water and water systems for injection include components, control techniques and similar procedures. The quality attributes of both waters differ only in the presence of a requirement of bacterial endotoxin for water for injection and in its preparation methods, at least in the last stage of preparation. The similarities in quality attributes provide a design of water systems to meet any of the requirements. The critical difference is the degree of control of the system and the final steps necessary to ensure the removal of bacterial and bacterial endotoxins. Pharmaceutical water production employs sequential unit operations (processing steps) that address specific water quality attributes and protect the operation of subsequent treatment steps. A typical evaluation process for selecting an adequate water quality for a given pharmaceutical purpose is shown in the decision tree in Figure 2. This diagram can be used to assist in defining requirements for specific water use and in selecting unit operations. The operation of the final unit used to produce water for injection is limited to distillation or other processes equivalent to or superior to distillation in the removal of chemical impurities, as well as microorganisms and their components. Distillation has a long history of reliable performance and can be validated as a unitary operation for the production of Injection Water, but other technologies or combinations of technologies can be validated as being equivalently effective. Other technologies, such as ultrafiltration after another chemical purification process, can be suitable in the production of Injection Water if they can be shown through validation as effective and reliable as distillation. The advent of new materials for older technologies, such as reverse osmosis and ultrafiltration, which allow intermittent or continuous operation at high microbial temperatures, show promise of a valid use in the production of Water for Injection. The validation plan should be designed to establish the adequacy of the system and provide a complete understanding of the purification mechanism, achievement of operating conditions, pre-treatment required, and the most likely modes of failure. It is also necessary to demonstrate the effectiveness of the monitoring scheme and establish documentation and qualification requirements for system validation maintenance. Tests performed in a pilot facility can be valuable in defining operational parameters and expected water quality and identifying failure modes. However, the qualification of the unit-specific operation can only be performed as part of the validation of the installed operating system. The selection of unit-specific operations and design characteristics for a water system should take into account the quality of the feed water, the technology chosen for subsequent processing steps, the extent and complexity of the water distribution system, and the mandatory compendium requirements. For example, in the design of a water system for injection, the final process (distillation or any other validated process is used according to the monograph) should have an effective capacity to reduce bacterial endotoxin and should be validated. The following is a brief description of the selected unit operations and the operations and validation concerns to them. Not all unit operations are discussed, not all potential problems are resolved. O O is to highlight issues that focus on the parameters of design, installation, operation, maintenance and monitoring that facilitate the validation of the water system. The purpose of prefiltration — also referred to as initial, coarse, or depth filtration — is to remove solid contaminants up to a size of 7 to 10 µm from the inlet source water supply and protect downstream system components from particles that can inhibit equipment performance and shorten its service life. This coarse filtration technology mainly uses sieving effects for particle capture and a depth of filtration medium that has a high dirt load capacity. Such filtration units are available in a wide range of designs and for various applications. Removal efficiencies and capabilities differ significantly, from granular bed filters such as multimedia or sand for larger water systems to depth cartridges for smaller water systems. Drive and system configurations vary widely in filter media type and process location. Granular prefilters or cartridges are often located on the head or near the head of the water pretreatment system prior to unit operations designed to remove the source water disinfectants. This location, however, does not exclude the need for periodic microbial control because the biofilm can still proliferate, although at a slower rate in the presence of water disinfectants of origin. Design and operational issues that can affect the performance of depth filters include filter media channeling, slable blockage, microbial growth, and filtermedia loss during improper washing. Control measures involve pressure and flow monitoring during the use and back washing, sanitization and replacement of filter media. An important design concern is filter sizing to prevent channeling or loss of media resulting from inadequate water flow rates, as well as proper scaling to minimize excessively frequent or infrequent replacement of the scribble or cartridge filter. Carbon beds activated granular adsorb low molecular weight organic material and oxidizing additives such as chlorine and chlorine and chloromine compounds, removing them from water. They are used to achieve certain quality attributes and to protect against the reaction with downstream stainless steel surfaces, resins and membranes. Key operational concerns regarding activated carbon beds include the propensity to support bacterial growth, hydraulic plumbing potential, organic adsorption capacity, appropriate water flow rates and contact time, inability to be regenerated in situ, and the shedding of bacteria, endotoxins, organic chemicals and fine carbon particles. The may involve monitoring water flow rates and differential pressures, sanitizing with hot water or steam, backwashing, testing for adsorption capacity and frequent carbon bed replacement. If the activated carbon bed is intended for organic reduction, it may also be appropriate to monitor tocefffluents and effluents. Itis Itis note that the use of steam for carbon bed hygiene is often incompletely effective due to steam channeling rather than even permeation through the bed. This phenomenon can usually be avoided by using hot water hygiene. It is also important to note that the development of microbial biofilms on the surface of granular carbon particles (as well as in other particles, as found in deionizing beds and even multimedia beds) can cause adjacent bed beads to stick together. When large masses of granules are agglomerated in this way, normal back washing parameters and bed fluidity may not be sufficient to disperse them, leading to ineffective removal of trapped debris, loose biofilm and penetration of microbial control conditions (as well as regenerating chemicals, as well as in the case of agglomerada deionizing resins). Alternative technologies for activated carbon beds can be used to prevent your microbial problems, such as disinfectant neutralizing chemical additives and regenerated organic cleaning devices. However, these alternatives do not work by the same mechanisms as activated carbon, may not be as effective in removing disinfectants and some organics, and have a different set of operational concerns and control measures that can be almost as problematic as activated carbon beds. Chemical additives are used in water systems (a) to control microorganisms through the use of sanitizers such as chlorine and ozone compounds, b To increase the removal of suspended solids by means of flocculan agents, (c) remove chlorine compounds, (d) to avoid sizing on reverse osmosis membranes and (e) adjust pH for a more effective removal of carbonate compounds and ammonia by reverse osmosis. These additives do not constitute added substances, provided that they are removed by subsequent processing steps or are absent from finished water. Control of additives to ensure continuously effective concentration and subsequent monitoring to ensure that its removal is designed in the system and included in the monitoring program. Organic cleaning devices use weakly basic macroreticular anion exchange resins capable of removing organic material and endotoxins from water. They can be regenerated with appropriate biocidal caustic brine solutions. Operational concerns are associated with organic cleaning capacity, particles, chemical and microbiological inlay of resin reactive surface, flow rate, regeneration frequency and resin fragment spillage. Control measures include toc testing of influential and effluent, backwashing, hydraulic performance monitoring and use of downstream filters to remove resin fines. Water softeners may be located upstream or downstream of removal units They use sodium-based cation-exchange-based resins to remove water hardness ions, such as calcium and magnesium, that could foul or interfere with the performance of downstream processing equipment, such as how osmosis membranes, deionization devices and distillation units. Water softeners can also be used to remove other lower affinity bindings, such as ammonium ion, which can be released from chloromine disinfectants commonly used in drinking water and which may otherwise undergo other downstream unit operations. If ammonium removal is one of its purposes, the softener should be located downstream of the disinfectant removal operation, which in itself can release ammonium from neutralized chloromine disinfectants. The water softener resin beds are regenerated with concentrated sodium chloride (brine) solution. Concerns include the proliferation of microorganisms, channeling caused by the agglomeration of resin particle biofilms, adequate water flow rates and contact time, ion exchange capacity, organic and particulate resin fouling, organic leaching of new resins, fracture of resin beads, degradation of resin by excessively chlorinated water, and contamination of brine solution used for regeneration. Control measures involve water recirculation during periods of low water use, periodic sanitization of the resin and brine system, use of microbial control devices (e.g., UV light and chlorine), location of the unit upstream of the disinfectant removal step (if used only for softening), adequate regeneration frequency, chemical effluent monitoring (e.g. , hardness ions and possibly ammonium) and downstream filtration to remove resin fines. If a softener is used for removal of ammonium from the source water containing chloroamine, then the capacity, contact time, the inlay of the resin surface, the pH and the regeneration frequency are very important. Deionization (DI) and continuous electrodeionization (CEDI) are effective methods to improve the attributes of chemical quality of water by removing caingos and anions. DI systems have loaded resins that require periodic regeneration with acid and base. Typically, cataic resins are regenerated with hydrochloric or sulfuric acid, which replaces the positive ions captured by hydrogen ions. Anionic resins are regenerated with sodium or potassium hydroxide, which replaces negative ions captured by hydroxide ions. As the free endotoxin is negatively charged, there is some removal of the endotoxin achieved by the anionic resin. Both regenerating chemicals are biocides and offer a microbial control measure. The system can be designed so that the casing and anion resins are in separate or twin beds or can be mixed to form a mixed bed. Twin beds are easily regenerated, but deionize water less efficiently than mixed beds, which have a considerably more complex regeneration process. Rechargeable resin containers can also be used this end. The CEDI system uses a combination of mixed resin, selectively permeable membranes and an electrical charge, providing continuous flow (product concentrate and waste) and continuous regeneration. Water enters both the resin section and the waste section (concentrates). (concentrated). through the resin, it is deionized to become water from the product. The resin acts as a conductor, allowing the electrical potential to drive the caries and anions captured through the resin and membranes suitable for concentration and removal in the wastewater flow. The electrical potential also stifies water in the resin (product) section into hydrogen and hydroxide ions. This allows continuous resin regeneration without the need for regenerative additives. However, unlike conventional deionization, CEDI units should start with water that is already partially purified because they generally cannot produce purified water quality when starting with the heavier ion load of unpurified source water. Concerns with all forms of deionization units include microbial and endotoxin control, chemical additive impact on resins and membranes, and resin loss, degradation and incrustion. Specific issues for DI units include frequency of regeneration and completeness, plumbing, caused by biofilm agglomeration of resin particles, organic leaching of new resins, complete separation of resin for mixed bed regeneration, and mixture of air contamination (mixed beds). Control measures vary, but typically include recirculation loops, microbial control of effluents by UV light, conductivity monitoring, resin testing, microporous filtering of mixing air, microbial monitoring, frequent regeneration to minimize and control the growth of microorganisms, sizing equipment for proper water flow and contact time, and use of high temperatures. The internal distributor and regeneration pipe for mixed bed units must be configured to ensure that regeneration chemicals come into contact with all internal bed and pipe surfaces and resins. Rechargeable containers can be the source of contamination and should be carefully monitored. Full knowledge of previous resin use, minimum storage time between regeneration and use, and proper hygiene procedures are critical factors that ensure good performance. Reverse osmosis (RO) units employ semipermeable membranes. The pores of RO membranes are actually intersegmental spaces between polymer molecules. They are large enough for the permeation of water molecules, but too small to allow the passage of hydrated chemical ions. However, many factors, including pH, temperature and differential pressure throughout the membrane affect the selectivity of this permeation. With the proper controls, RO membranes can achieve chemical, microbial and quality improvements of endotoxins. Process flows consist of water supply, product water (permeated) and waste water (waste water). Depending on the source water, pretreatment variations and system configuration and may be required to achieve the desired performance and reliability. One of the main factors that affect the performance of THE is the permeated recovery rate, that is, the amount of water passing through the membrane in relation to the amount rejected. This is influenced by the various factors, but most pressure of the pump. 75% recoveries are typical, and can perform a log purification of 1 to 2 of most impurities. For most feed waters, this is usually not enough to meet the conductivity specifications of purified water. A second passage of this water permeated by another stage of RO usually achieves the necessary permeated purity if other factors such as pH and temperature have been adequately adjusted and ammonia from chloramine source water has been previously removed. Increasing recoveries with higher pressures in order to reduce the volume of water rejected will lead to reduced permeated purity. If increased pressures are required over time to achieve the same permeation flow, this is an indication of partial membrane blockage that needs to be corrected before it becomes irreversibly immisgotten, and expensive membrane replacement is the only option. Other concerns associated with the design and operation of RO units include membrane materials extremely sensitive to sanitized agents and the incrusation of particulate, chemical and microbial membranes; membrane and seal integrity; the passage of dissolved gases such as carbon dioxide and ammonia; and the volume of waste water, particularly where water discharge is heavily regulated by local authorities. Failure to maintain the integrity of the membrane or seal will result in contamination of the product's water. Control methods involve proper pretreatment of influential water flow, proper selection of membrane materials, integrity challenges, membrane design and heat tolerance, periodic hygiene and monitoring of differential pressures, conductivity, microbial levels and TOC. The development of RO units that can tolerate the hygiene of water temperatures, as well as operate efficiently and continuously at high temperatures, has added much to its microbial control and the prevention of biofouling. RO units can be used alone or in combination with DI and CEDI units, as well as ultrafiltration for operational and quality improvements. Ultrafiltration is a technology most often employed in pharmaceutical water systems to remove endotoxins from a water flow. It can also use semi-permeable membranes, but unlike RO, they typically use polysulfone membranes whose intersegmental pores were purposely exaggerated during their manufacture, preventing polymer molecules from reaching their smallest proximity to balance. Depending on the level of equilibrium control during its manufacture, membranes with different molecular weight cuts can be created in such a way that molecules with molecular weights above these cut ratings are rejected and cannot penetrate the filtration matrix. Ceramic ultrafilters are another molecular sieve technology. Ceramic ultrafilters are and extremely durable, invertable, chemically clean and steam sterilized. However, they may require higher operating pressures than membrane-like ultrafilters. All ultrafiltration devices work by a molecular sieve principle. Ultrafilters with molecular weight cutting ratings in the range of 10,000 to 20,000 Da are typically used in water systems to remove endotoxins. This technology can be suitable as an intermediate or final purification step. Similar to RO, successful performance depends on water pretreatment by upstream unit operations. Concern issues for ultrafilters include compatibility of membrane material with heat and sanitization agents, membrane integrity, particle and microorganism incrusation, and seal integrity. Control measures involve medium filtration selection, sanitization, flow design (sac vs. tangential alley), integrity challenges, regular cartridge changes, high feed water temperature, and OCD monitoring and differential pressure. Additional flexibility in operation is possible based on how ultrafiltration units are organized, such as in parallel configurations or series. Care should be taken to avoid stagnant water conditions that may promote the growth of microorganisms in backup or standby units. Modified load modified filters are usually microbially retentive filters that are treated during their manufacture to have a positive load on their surfaces. Microbial retentive filtration will be described in a subsequent section, but the significant characteristic of these membranes is their electrostatic surface charge. These loaded filters can reduce the levels of dondotoxin in the fluids that pass through them by their adsorption (due to the negative charge of dodotoxin) on the membrane surfaces. Although ultrafilters are most often used as a unitary operation for the removal of endotoxins in water systems, load-modified filters can also have a place in removing endotoxins, particularly where upstream available pressures are not sufficient for ultrafiltration and for a single short-term use. Load-modified filters can be difficult to validate for long- or large-volume endotoxin retention. Although its retention of purified standard endotoxin can be well characterized, its ability to retain natural endotoxins is difficult to measure. However, the utility could be demonstrated and validated as short-term single-use filters at points of use in water systems that are not designed for endotoxin control or where only a polysing endotoxin (removal of only slight or occasional endotoxin levels) is required. Control and validation concerns include volume and duration of use, flow rate, conductivity and purity of water, and constancy and concentration of endotoxin levels being removed. All of these factors may have to be evaluated and challenged before using this approach, making this an application difficult to validate. Even so, there may be a possible need for additional backup endotoxin testing both upstream and downstream of the filter. Microbial-retentive membrane filters of microbial-retentive filtration have experienced an evolution of understanding in the past that caused previously maintained theoretical retention mechanisms to be reconsidered. These filters have a more effective pore size than ultrafilters and are intended to prevent microorganisms and particles of similar size from passing through without unduly restricting flow. This type of filtration is widely used within water systems to filter bacteria from both water and compressed gases, as well as for ventilation filters in tanks and environments and other unit operations. However, the properties of microorganisms in the water system seem to challenge the microbial retention of a water filter with phenomena absent from other aseptic filtration applications, such as sterilization of pharmaceutical formulation filters before packaging. In the latter application, sterilizing grade filters are generally considered to have an assigned rating of 0.2 or 0.22 µm. This rather arbitrary classification is associated with filters that have the ability to maintain a high-level challenge of a specially prepared inoculum of brevundimones (ex-Pseudomonas) miniature. It is a small microorganism originally isolated decades ago from a product that had been filtered sterilized using a filter rated at 0.45 µm. Other studies have revealed that a percentage of cells of this microorganism could reproducibly penetrate 0.45-µm sterilizing filters. Through the historical correlation of B. diminuta retaining tighter filters, considered twice as good as 0.45-µm filter, assigned classifications of 0.2 or 0.22 µm with its successful use in sterilization of product solution filters, both this filter classification and the associated high level B. diminuta challenge have become the current benchmarks for filtration sterilization. New evidence now suggests that for microbial-retentive filters used for pharmaceutical water, B. diminuta may not be the best model microorganism. An archaic understanding of microbial retentive filtration would lead to one matching the classification of a filter with the false impression of a simple sieve or screen that absolutely retains particles sized in the filter classification or above the filter. A current understanding of the mechanisms involved in microbial retention and the variables that can affect these mechanisms has generated a much more complex interaction of phenomena than previously understood. A combination of simple sieve retention and surface adsorption are now known to contribute to microbial retention. All interact to create some unusual and surprising retention phenomena for microorganisms of the water system: the variability in the range and average sizes of pores created by the various membrane manufacturing processes, the variability of surface chemistry and three-dimensional structure related to the different polymers used in these and the size and surface properties of the microorganism intended to be retained by the filters. B. miniature may not be the best challenge of microorganisms to demonstrate bacterial retention for filters rated from 0.2 to 0.22 µm for use in water water because it seems to be more easily retained by these filters than some flora of the water system. The well-documented appearance of microorganisms of the water system on the downstream sides of about 0.2 to 0.22-µm of filters classified after a relatively short period of use seems to support that some penetration phenomena are in action. Unknown is whether this downstream appearance is caused by a blow-through or some other passing phenomenon as a result of tiny or less sticky cell cells, or by a phenomenon of growth through as a result of cells hypothetically replicating their way through the pores to the downstream side. Whatever the penetration mechanism, membranes evaluated from 0.2 to 0.22 µm may not be the best

choice for some uses of the water system. The success of microbial retention in water systems has been reported with the use of filters from some manufacturers arbitrarily rated as 0.1 µm. There is a general agreement that, for a given manufacturer, its rated filters of 0.1 µm are tighter than their rated filters from 0.2 to 0.22-µm. However, comparatively evaluated filters from different manufacturers in water filtration applications may not work equivalently due to the different filter manufacturing processes and the non-standard microbial retention challenge processes currently used to define the filter rating of 0.1-µm. It should be noted that the use of evaluated membranes of 0.1-µm usually results in a sacrifice in the flow rate compared to membranes from 0.2- to 0.22-µm, so that any membranes are chosen for a water system application, the user should verify that the membranes are suitable for their intended application, period of use and process of use , including flow rate. For microbial retentive gas filtrations, the same sieve and adsorptive retention phenomena are in action as in liquid filtration, but the adsorptive phenomenon is enhanced by additional electrostatic interactions between particles and filter matrix. These electrostatic interactions are so strong that particle retention for a given filter classification is significantly more efficient in gas filtration than in water filtration or product solution. These additional adsorptive interactions make the filters classified at 0.2 to 0.22 µm unquestionably suitable for microbial retentive gas filtrations. When microbially retentive filters are used in these applications, the membrane surface is typically hydrophobic (non-water-wetted). A significant area of concern for gas filtration is blocking the tank openings by condensed water vapor, which can cause mechanical damage to the tank. Control measures include electrical or steam tracking and a self-draining orientation of the ventilation filter housings to prevent condensate build-up from However, a continuously high filter temperature will have an oxidative toll on the components of the filter polypropylene, so that sterilization of the unit before initial use, and periodically thereafter, as well as regular visual inspections, integrity tests and changes are recommended control methods. Em Em applications, microbial retentive filters can be used downstream of unit operations that tend to release microorganisms or upstream of unit operations sensitive to microorganisms. Microbial retentive filters can also be used to filter the water supply of the distribution system. It should be noted that regulatory authorities allow the use of microbial retentive filters within distribution systems or even at points of use if they have been properly validated and are properly maintained. A point-of-use filter should only be intended to polish the microbial quality of a well-maintained system and not serve as the main microbial control device. The effectiveness of microbial control measures of the system can only be evaluated by sampling the water upstream of the filters. As an additional measure of protection, inline UV lamps, properly sized for the flow rate (see Hygiene), can be used only upstream of microbial retentive filters to inactivate microorganisms before their capture by the filter. This tandem approach tends to greatly delay potential microbial penetration phenomena and can substantially extend filter life. The use of low pressure UV lights that emit a wavelength of 254 nm for microbial control is discussed under Sanitization, but the application of UV light in chemical purification is also emerging. This wavelength of 254 nm is also useful in the destruction of ozone. With intense emissions at wavelengths of around 185 nm (as well as at 254 nm), medium pressure UV lights demonstrated usefulness in the destruction of chlorine containing disinfectants used in the source water, as well as for temporary stages of water pretreatment. High intensities of this wavelength alone or in combination with other oxidizing sanitizers, such as hydrogen peroxide, have been used to lower OCD levels in recirculating distribution systems. Organics are typically converted into carbon dioxide, which balances into bicarbonate, and incompletely oxidized carboxylic acids, both of which can be easily removed by polishing ion exchange resins. Areas of concern include adequate UV intensity and residence time, gradual loss of UV emissivity with lamp age, gradual formation of UV-absorbing film on the surface of water contact, incomplete photodegradation during unforeseen source water hyperclonation, ammonia release from chloromine photodegradation, failure of the ammonium UV lamp, and conductivity degradation in distribution systems using 185-nm UV lights. Control measures include regular inspection or emissivity alarms to detect lamp failures or film occlusions, regular cleaning and cleaning of the UV lamp sleeve, downstream chlorine detectors, downstream polishing deionizers, and regular replacement (approximately annual Distillation units provide chemical and microbial purification through thermal vaporization, mist elimination and water vapor condensation. A variety of designs are available, including unique effect, multiple effect and steam steam The last two configurations are typically used on larger systems due to their generation capacity and efficiency. Distilled water systems require different feed water controls than required by membrane systems. For distillation, the prior removal of hardness and silica impurities that may soil or corrode heat transfer surfaces should be considered, as well as the prior removal of those impurities that could volatize and condense together with water vapor. Despite general perceptions, even the best distillation process cannot allow the absolute removal of contaminant ions and endotoxins. Most stills are recognized as capable of performing at least a 3 to 4 log reduction in these concentrations of impurity. Areas of concern include the transport of volatile organic impurities, such as trihalomethanes (see Water Supply and Power Considerations) and gaseous impurities such as ammonia and carbon dioxide, elimination of defective mist, evaporator flooding, inadequate flooding, stagnant water in condensers and evaporators, pump and compressor seal design, pinbone evaporator and condenser leaks, and conductivity variations (quality) during start-up and operation. Control methods may involve preliminary decarbonization steps to remove both dissolved carbon dioxide and other volatile or non-condensable impurities; reliable elimination of mist to minimize the intake of feed water droplets; visual or automated indication of high water level to detect flooding and boil the boiler; use of sanitary pumps and compressors to minimize microbial contamination and lubricant of water and condensate; adequate drainage during inactive periods to minimize microbial growth and associated endotoxin accumulation in boiler water; knock down the control to limit the effect of impurity concentration in the boiler to manageable levels; Online conductivity detection with automated diversion to waste to prevent unacceptable water at startup or even malfunction from entering the finished water distribution system; and periodic integrity tests for pinhole leaks to routinely ensure that condensate is not compromised by non-volatized water contaminants. Storage tanks are included in water distribution systems to optimize the capacity of processing equipment. Storage also enables routine maintenance within the pretreatment train, maintaining continuous supply to meet manufacturing needs. Design and operation considerations are necessary to prevent or minimize biofilm development, minimize corrosion, assist in the use of chemical sanitization of tanks and safeguard mechanical integrity. These considerations may include the use of closed tanks with smooth, the ability to spray space to the tank head using spray balls in recirculating loop returns and the use of heated tanks, setbacks/isolates. This minimizes the development of corrosion and biofilm and assists in thermal and chemical hygiene. Storage tanks require ventilation to compensate for the dynamics of change Levels. This can be accomplished with a properly oriented filter housing and thermal lysing equipped with a hydrophobic microbial retentive membrane filter affixed to atmospheric ventilation. Alternatively, an automatic membrane-filtered compressed gas coverage system can be used. In both cases, rupture discs equipped with a rupture alarm device should be used as an additional protection for the mechanical integrity of the tank. Areas of concern include microbial growth or corrosion due to irregular or incomplete hygiene and microbial contamination by unarmed rupture disc failures caused by condensed ventilation filters. The configuration of the distribution system should allow the continuous flow of water into the pipe by means of recirculation. The use of systems or segments of systems not refuse, without output or unidirectional should be avoided whenever possible. If this is not possible, these systems should be periodically washed and monitored more closely. Experience has shown that continuously recirculated systems are easier to maintain. Pumps should be designed to provide fully turbulent flow conditions to facilitate complete heat distribution (for sanitized hot water systems) as well as a complete chemical distribution. The turbulent flow also seems to slow the development of biofilms or reduce the tendency of these biofilms to release bacteria into the water. If redundant pumps are used, they should be configured and used to prevent microbial contamination of the system. Components and distribution lines must be inclined and equipped with drainage points so that the system can be completely drained. In stainless steel distribution systems where water is circulated at a high temperature, dead legs and low flow conditions should be avoided, and valve connection points should have length-to-diameter ratios of six or less. If constructed of heat-tolerant plastic, this proportion should be even lower to avoid cold spots where biofilm development could occur. In room temperature distribution systems, particular care should be exercised to avoid or minimize dead leg relationships of any size and provide complete drainage. If the system is intended to be sanitized by steam, sloping and low-point drainage is crucial to the successful removal and sanitization of condensate. If the drainage of components or distribution lines is intended as a microbial control strategy, they must also be configured to be completely dry using dry compressed air (or nitrogen, if appropriate employee safety measures are used). Drained but still moist surfaces will still withstand microbial proliferation. The water outlet of the distribution system is not be returned to the system without first passing through the entire or whole of the purification train. The distribution project should include placing sampling valves in the storage tank and other locations, such as on the return line of the recirculating water system. Where possible, the primary sampling sites for water should be the that deliver water to points of use. Direct connections to auxiliary processes or equipment should be designed to prevent reverse flow to the controlled water system. Hoses and heat exchangers that are connected to points of use to provide water for a specific use should not chemically or microbiologically degrade water quality. The distribution system should allow hygiene for the control of microorganisms. The system can be continuously operated under hygiene conditions or sanitized periodically. INSTALLATION, BUILDING MATERIALS AND SELECTION OF COMPONENTS Installation techniques are important because they can affect the mechanical, corrosive and sanitary integrity of the system. The attitude of valve installation should promote gravitational drainage. Pipe supports must provide suitable slopes for drainage and should be designed to support the pipe properly under the worst thermal and flow conditions. Methods of connecting system components, including operating units, tanks, and distribution pipes, require careful attention to avoid potential problems. Stainless steel welds must provide reliable, internally smooth and corrosion-free joints. Low carbon stainless steel, compatible wire filler, when needed, inert gas, automatic welding and inspection machines and regular documentation help ensure acceptable weld quality. Follow-up cleaning and passivation is important for removing contamination and corrosion products and restoring passive corrosion-resistant surface. Plastic materials can be fused (welded) in some cases and also require smooth and uniform internal surfaces. Adhesive glues and solvents should be avoided due to the potential for voids and extractables. Mechanical joining methods, such as flange fittings, require care to avoid creating compensations, gaps, penetrations, and voids. Control measures include good alignment, appropriately sized joints, proper spacing, uniform sealing force, and avoiding threaded fittings. Building materials must be selected to be compatible with control measures such as hygiene, cleaning, and passivation. Temperature rating is a critical factor in choosing appropriate materials, as surfaces may be required to handle high operating and hygiene temperatures. If chemicals or additives are used to clean, control or sanitize the system, materials resistant to such chemicals or additives should be used. Materials should be able to handle turbulent flow and high speeds without corrosion-resistant film wear, such as the passive surface of stainless steel chrome oxide. Finishing on metallic materials such as stainless steel, whether a refined finish of the mill, polished to a specific grain, or electropolished treatment, should complement the design of the system and provide satisfactory resistance to corrosion and microbial activity, as well as chemical sanitizeability. Auxiliary equipment and accessories that seals, joints, diaphragms, filter media and membranes should exclude materials that allow the possibility of extractables, shedding and microbial activity. Electrical materials exposed to stainless steel surfaces should be chloride-free to prevent the phenomenon of stress corrosion cracking that can lead to system contamination and destruction of critical tanks and system components. Specifications are important to ensure proper selection of materials and serve as a reference for the qualification and maintenance of the system. Information such as stainless steel mill reports and composition reports, classifications and material handling capabilities for non-metallic substances should be reviewed for suitability and retained for reference. The selection of components (auxiliary equipment) should be made with the guarantee that it does not create a source of contamination intrusion. Heat exchangers should be built to prevent leaks from heat transfer medium to pharmaceutical water and, for heat exchanger designs where prevention may fail, there should be a means of detecting leaks. Pumps must be sanitary in design with seals that prevent water contamination. Valves must have smooth internal surfaces with the seat and closing device exposed to the action of water discharge, as occurs in diaphragm valves. Valves with pocket areas or closing devices (e.g., ball, plug, gate, globe) that move in and out of the flow area should be avoided. Microbial control in water systems is achieved mainly through hygiene practices. Systems can be sanitized using thermal or chemical media. Thermal approaches to system hygiene include periodic or continuous hot water and the use of steam. Temperatures of at least 80 are most commonly used for this purpose, but continuous recirculation water of at least 65 has also been effectively used in insulated stainless steel distribution systems when paying attention to the uniformity and distribution of such self-sanitizing temperatures. These techniques are limited to systems compatible with the highest temperatures required to achieve hygiene. Although thermal methods control the development of biofilms by continuously inhibiting their growth or, in intermittent applications, killing microorganisms within biofilms, they are not effective in removing established biofilms. Dead but intact biofilms can become a source of nutrients for the rapid growth of the biofilm after hygiene conditions are removed or disrupted. In such cases, a combination of routine thermal and periodic supplementation with chemical hygiene may be more effective. The more frequent the thermal hygiene, the more likely the development and regrowth of the biofilm. chemicals, when compatible, can be used in a wider variety of building materials. These methods typically employ oxidizing agents such as halogenated compounds, hydrogen peroxide, ozone, peracetic acid, or of this same. Halogenated compounds are effective disinfectants, but are difficult to clean from the system and can leave biofilms intact. Compounds such as hydrogen peroxide, ozone and peracetic acid oxidize bacteria and biofilms forming reactive peroxides and free radicals (nobly hydroxyl radicals). The short half-life of ozone in particular, and its limitation in reachable concentrations require it to be added continuously during the sanitization process. Hydrogen peroxide and ozone rapidly degrade to water and oxygen; peracetic acid degrades to acetic acid in the presence of UV light. In fact, the ease of degradation of ozone to oxygen using 254 nm UV lights at points of use allows it to be used more effectively on a continuous basis to provide continuous sanitizing conditions. Inline UV light at a wavelength of 254 nm can also be used to continuously sanitize the water circulating in the system, but these devices must be properly sized for the flow of water. Such devices inactivate a high percentage (but not 100%) microorganisms that flow through the device, but cannot be used to directly control the existing biofilm upstream or downstream of the device. However, when together with conventional thermal or chemical hygiene technologies or located immediately upstream of a microbially retentive filter, it is more effective and can prolong the interval between system hygienes. It is important to note that microorganisms in a well-developed biofilm can be extremely difficult to kill, even by aggressive oxidizing biocides. The less developed and therefore thinner the biofilm, the more effective the biocide action is. Therefore, the optimal control of biocide is achieved by the frequent use of biocides that does not allow the significant development of biofilm between treatments. Hygiene steps require validation to demonstrate the ability to reduce and maintain microbial contamination at acceptable levels. The validation of thermal methods should include a heat distribution study to demonstrate that hygienic temperatures are achieved throughout the system, including the body of point-of-use valves. The validation of chemical methods requires the demonstration of appropriate chemical concentrations throughout the system, exposure to all wet surfaces, including the body of point-of-use valves, and complete removal of the system sanitant at completion of treatment. The validation of methods for the detection and quantification of residues of the sanitant or its objectionable degrading is an essential part of the validation program. The frequency of hygiene should be supported by the results of microbial monitoring of the system. Conclusions derived from the trend analysis of microbiological data should be used as a maintenance alert mechanism. The frequency of hygiene established in such a way that the system operates in a state of microbiological control and does not routinely exceed alert levels (see Alert and Action Levels and OPERATION, MAINTENANCE AND CONTROL A preventive maintenance program must be established to ensure that the water system remains in a state of control. The program should include (1) procedures for system operation, (2) monitoring programs for critical quality attributes and operating conditions, including calibration of critical instruments, (3) schedule for periodic hygiene, (4) preventive maintenance of components, and (5) control of changes in the mechanical system and operating conditions. Operational procedures — The procedures for operating the water system and performing routine maintenance and corrective actions should be written, and they should also define the point at which action is required. The procedures should be well documented, detail the function of each work, assign who is responsible for performing the work and describe how the work should be conducted. The effectiveness of these procedures should be assessed during the validation of the water system. Monitoring Program — Critical quality attributes and operational parameters must be documented and monitored. The program may include a combination of inline sensors or automated instruments (e.g. for OCD, conductivity, hardness and chlorine), automated or manual documentation of operational parameters (such as flow rates or pressure drop in a carbon bed, filter or RO unit), and laboratory tests (e.g., total microbial count). The frequency of sampling, the requirement to evaluate the test results and the need to initiate corrective actions should be included. Hygiene — Depending on the system design and the selected operating units, routine periodic hygiene may be required to keep the system in a microbial control state. The technologies for hygiene are described above. Preventive Maintenance - A preventive maintenance program must be in place. The program shall establish what preventive maintenance to be carried out, the frequency of maintenance work and how the work should be documented. Change control — Mechanical configuration and operating conditions must be controlled. The proposed changes should be assessed for their system-throughout impact. The need to requalify the system after the changes must be determined. After the decision to modify a water system, the affected drawings, manuals and procedures should be reviewed. Water systems should be monitored at a sufficient frequency to ensure that the system is under control and continues to produce water of acceptable quality. Samples should be taken at representative locations within the processing and distribution system. The established sampling frequencies should be based on system validation data and should cover critical areas, including unit operating locations. The sampling plan should be desired attributes of the water being sampled. For example, injection water systems due to their most critical microbiological requirements may require a rigorous sampling frequency. Analyses of water samples generally serve two purposes: in-process control assessments and final quality control assessments. In-process control analyses are generally focused on the attributes of water within the system. Quality control is mainly concerned with the attributes of the water delivered by the system to its various uses. The latter usually employs some type of transfer device, often a flexible hose, to fill the gap between the distribution system's point-of-use valve and the actual location of water use. The question of the location of the sample collection and the sampling procedure is often debated because of the typically mixed use of the data generated from the samples, both for in-process control and for quality control. In these situations of single sample use and mixed data, the worst case scenario should be used. In other words, samples should be collected from points of use using the same delivery devices, such as hoses and procedures, such as preliminary hose or outlet discharge, as they are employed by the production of these points of use. When the points of use themselves cannot be sampled, such as hard pipe connections to the equipment, special sampling ports can be used. In all cases, the sample shall represent as close as possible the quality of the water used in production. If a point-of-use filter is used, sampling of water before and after the filter is required, as the filter will mask the microbial control achieved by the normal operating procedures of the system. Samples containing chemical hygiene agents require neutralization prior to microbiological analysis. Samples for microbiological analysis should be tested immediately, or properly refrigerated to preserve the original microbial attributes until the analysis can begin. Running water samples are only indicative of the concentration of plantonic (free floating) microorganisms present in the system. Biofilm microorganisms (those linked to the surfaces of the water system) are usually present in greater numbers and are the source of the plankton population recovered from the capture samples. Microorganisms in biofilms represent a continuous source of contamination and are difficult to directly show and quantify. Consequently, the plankton population is generally used as an indicator of system contamination levels and is the basis for system Alert and Action Levels. The consistent appearance of elevated plankton levels is usually an indication of advanced development of biofilms that need corrective control. The control and hygiene of the system are fundamental in the control of biofilm formation and the consequent plankton population. Sampling for chemical analyses is also for in-process control and for quality control purposes. However, unlike microbial analyses, chemical analyses can be and are often performed using online instrumentation. Such online tests have unambiguous control purposes in process because they are not performed in the water supplied from the system. System. unlike microbial attributes, chemical attributes are generally not significantly degraded by hoses. Therefore, through verification tests, it may be possible to show that the chemical attributes detected by online instrumentation (in-process testing) are equivalent to those detected at the ends of point-of-use hoses (quality control test). This recreates a single sample usage and mixed data usage scenario. It is much better to operate instrumentation in a continuous mode, generating large volumes of data in process, but only by using a small defined sampling of this data for QC purposes. Examples of acceptable approaches include the use of higher values for a given period, the most weighted average for a given period (of fixed or rolling subtimes), or values in a fixed daily time. Each approach has advantages and disadvantages over the complexity of calculating and reflecting continuous quality, so the user must decide which approach is most appropriate or justifiable. The chemical attributes of Purified Water and Water for Injection have been specified by a series of chemistry tests for various specific and non-specific attributes with the intention of detecting chemical species indicative of incomplete or inadequate purification. Although these methods might have been considered inadequate to control the quality of these waters, they nevertheless stood the test of time. This was partly because the functioning of water systems was, and still is, based on online conductivity measurements and generally thought-out specifications to prevent the failure of these archaic tests of chemistry attributes. USP has moved away from these chemical attribute tests for contemporary analytical technologies for bulk water Purified water and injection water. The intention was to update analytical technologies without strengthening quality requirements. The two contemporary analytical technologies employed were OCD and conductivity. The OCD test replaced the test of oxidizable substances that mainly targeted organic contaminants. A multi-agile conductivity test that detects ionic contaminants (mainly inorganic) replaced, with the exception of the heavy metal test, all inorganic chemical tests (i.e., Ammonia, Calcium, Carbon Dioxide, Chloride, Sulfate). The replacement of the heavy metals attribute was considered unnecessary because (a) the source water specifications (found in npdwr) for individual heavy metals were tighter than the approximate detection limit of the heavy metal test for USP XXII Injection Water and Purified Water (approximately 0.1 ppm), (b) contemporary water system building materials did not leach heavy metal contaminants , and (c) the test results for this attribute were uniformly negative — there was no confirmed occurrence of a Test failure (heavy metal test failure only with all other passing attributes) since current heavy metal drinking water standards were put into effect. However, the presence of heavy metals in Purified Water or Water for Injection can have dire consequences, their absence should at least be documented during the recommissioning and validation of the water system or through records of previous test results. Total solids and pH are the only tests not covered by conductivity tests. The test for total solids was considered redundant because non-selective conductivity and OCD tests were able to detect most chemical species besides silica, which could remain undetected in their colloidal form. Colloidal silica in Purified Water and Water for Injection is easily removed by most stages of water pretreatment and, even if present in water, does not constitute any medical or functional risk, except in extreme and rare situations. In such extreme situations, other attribute extremes are also susceptibleto detected. However, it is the user's responsibility to ensure fitness for use. If silica is a significant component in the source water, and the operations of the purification unit could be operated or failed and selectively allow silica to be released into the finished water (in the absence of conductivity-detectable co-contaminants), then either a silica type test or a type of total solids should be used to monitor and control this rare problem. The pH attribute was eventually recognized as redundant to the conductivity test (which included pH as the test aspect and specification); therefore, the pH was discarded as a separate attribute test. The logic used by USP to establish its conductivity specification took into account the conductivity contributed by the two less conductive attributes of Chloride and Ammonia, thus preventing its failure from having been performed these wet chemistry tests. In essence, the stage 3 conductivity specifications (see Water Conductivity 645) were established from the sum of the conductivities of chloride ion limit concentrations (from pH 5.0 to 6.2) and ammonia ions (from p 6.3 to 7.0), plus the inevitable contribution of other ions contributing to water conductivity (H^+ and $OH^–$), dissolved atmospheric CO_2 (such as $HCO_3^–$), and an electro-balancing amount of Cl^+ na^+, depending on pH-induced ion imbalance (see Table 1). The stage 2 conductivity specification is the lowest value in this table, 2.1 µS/cm. The Stage 1 specifications, designed primarily for online measurements, were derived essentially by adding the lowest values in the contributing ion columns for each of a series of tables similar to Table 1, created for each increment of 5 between 0 and 100. For example, the italic values in Table 1, the conductivity data table for 25, were summed to produce a conservative value of 1.3 µS/cm, the stage 1 specification for a non-naturalized water sample unnatural, which actually had a measured temperature of 25 to 29. Each increment table of 5 was treated in the same way to produce the individual values listed in the Phase 1 table (see Water Conductivity 645). Table one. Contributing Ion Conductivities of the Chloride–Ammonia Model as a Function of pH (in atmosphere-equilibrated water at 25) Conductivity (µS/cm) pH H^+ $OH^–$ $HCO_3^–$ $Cl^–$ Na^+ NH_4^+ Combined Conductivities Stage 3 Limit 5.0 3.49 0 0.02 1.01 0.19 0 4.71 4.7 5.1 2.77 0 0.02 1.01 0.29 0 4.09 4.1 5.2 2.20 0 0.03 1.01 0.38 0 3.62 3.6 5.3 1.75 0 0.04 1.01 0.46 0 3.26 3.3 5.4 1.39 0 0.05 1.01 0.52 0 2.97 3.0 5.5 1.10 0 0.06 1.01 0.58 0 2.75 2.8 5.6 0.88 0 0.08 1.01 0.63 0 2.60 2.6 5.7 0.70 0 0.10 1.01 0.68 0 2.49 2.5 5.8 0.55 0 0.12 1.01 0.73 0 2.41 2.4 5.9 0.44 0 0.16 1.01 0.78 0 2.39 2.4 6.0 0.35 0 0.20 1.01 0.84 0 2.40 2.4 6.1 0.28 0 0.25 1.01 0.90 0 2.44 2.4 6.2 0.22 0 0.31 1.01 0.99 0 2.53 2.5 6.3 0.18 0 0.39 0.63 0 1.22 2.42 2.4 6.4 0.14 0.01 0.49 0.45 0 1.22 2.31 2.3 6.5 0.11 0.01 0.62 0.22 0 1.22 2.18 2.2 06.6 0.09 0.01 0.78 0.04 1.22 2.14 2.1 6.7 0.07 0.01 0.99 0.27 1.22 2.56 0.562.6 6.8 0.06 0.01 1.24 0.56 1.22 3.09 3.1 6.9 0.04 0.02 1.56 0.93 1.22 3.. 77 3.8 7.0 0.03 0.02 1.97 0 1.39 1.22 4.63 4.6 As stated above, this quite radical change to use a conductivity attribute, as well as the inclusion of a TOC attribute allowed for online measurements. This was a major philosophical change and allowed large savings to be realized by industry. OCD and conductivity tests can also be performed offline in laboratories using collected samples, although sample collection tends to introduce opportunities for adventurous contamination that can cause false high readings. Online data collection is not, however, without challenges. Continuous reads tend to create bulky amounts of data where previously only a single data point was available. As indicated in Sampling Considerations, continuous data in process is excellent for understanding how a water system works during all of its various real-time use and maintenance events, but is too data for QC purposes. Therefore, one can use a justifiable fraction or an average of the data that still represent the overall quality of the water being used. Packed waters present a particular dilemma in relation to conductivity and OCD attributes. The package itself is the source of chemicals (inorganic and organic) that leach over time into the water and can be easily detected. The irony of organic leaching of plastic packaging is that when the test of oxidizing substances was the only test of organic contaminant for bulk and packaged waters, the insensitivity of this test to these organic leachings made its presence in water packed in high concentrations (often the Specification of OCD for bulk water) virtually undetectable. Similarly, glass containers can also leach inorganic, such as sodium, which are easily detected by conductivity but are not detected by wet chemical tests for water (other than pH or solids Most of these leachables are considered harmless by current perceptions and patterns in the fairly concentrations present. However, they effectively degrade the quality of the high purity waters placed in this packaging system. Some packaging materials contain more sandingthan others and may not be as suitable for holding water and maintaining its purity. Conductivity and OCD attributes tend to reveal more about sandable packaging than about the original purity of water. These allowed leachs could make the packed versions of bulk water originally equivalent essentially unsuitable for many uses where bulk water is perfectly adequate. The largest exogenous source of microbial contamination of bulk pharmaceutical water is the source or feed water. The quality of the feed water must at least meet the quality attributes of the Drinking Water for which the level of coliforms is regulated. A wide variety of other microorganisms, mainly Gram-negative bacteria, may be present in the incoming water. These microorganisms can compromise subsequent purification steps. Examples of other potential sources of microbial contamination include unprotected openings, faulty air filters, ruptured rupture discs, backflow of contaminated outlets, unofficially distribution system openings, including routine component replacements, inspections, repairs and expansions, improper drainage and air breaks, and replacement of activated carbon, deionizing resins, and regenerating chemicals. In these situations, exogenous contaminants may not be normal aquatic bacteria, but microorganisms from the soil or even of human origin. The detection of non-oral microorganisms may be an indication of a failure in the system component, which should trigger investigations that will remedy its source. Sufficient care should be given to the design and maintenance of the system in order to minimize microbial contamination of these exogenous sources. The unit's operations can be one of the main sources of endogenous microbial contamination. Microorganisms present in feed water can adsorption to the carbon bed, deionizing resins, filter membranes and other operating surfaces of the unit and initiate the formation of a biofilm. In a high purity water system, biofilm is an adaptive response of certain microorganisms to survive in this low nutrient environment. Downstream colonization can occur when microorganisms are spilled from surfaces colonized by existing biofilms and transported to other areas of the water system. Microorganisms can also connect to suspended particles such as carbon bed fines or fractured resin particles. When microorganisms become plant on them, they serve as a source of contamination for subsequent purification equipment (compromising their functionality) and distribution systems. Another source of endogenous microbial contamination the distribution system itself. Microorganisms can colonize pipe surfaces, rough welds, poorly aligned flanges, unidentified dead valves and legs, where they proliferate, forming a biofilm. The smoothness and composition of the surface may affect initial microbial adsorption rate, but once adsorbed, the development of biofilm, unless otherwise inhibited by sanitizing conditions, will occur regardless of the surface. Once formed, the biofilm becomes a continuous source of microbial contamination. Endotoxins are found and spilled lipolysis from the cellular envelope that is external to the cell wall of Gram-negative bacteria. Gram-negative bacteria that form biofilms can become a source of endotoxins in pharmaceutical waters. Endotoxins can occur as clusters of lipopolysaccharide molecules associated with living microorganisms, fragments of dead microorganisms, or polysaccharide slable around biofilm bacteria, or as free molecules. The free form of endotoxins can be released from the cellular surfaces of the bacteria that colonize the water system, or from the feed water that can enter the water system. Due to the multiplicity of endotoxin sources in a water system, the quantitation of endotoxin in a water system is not a good indicator of the level of abundance of biofilms within a water system. Endotoxin levels can be minimized by controlling the introduction of free endotoxins and microorganisms into feed water and minimizing microbial proliferation in the system. This can be accomplished through the normal action of exclusion or removal provided by various unit operations within the treatment system, as well as through the hygiene of the system. Other control methods include the use of ultrafilters or filters modified by load, inside or at the point of use. The presence of endotoxins can be monitored as described in the general test chapter Bacterial Endotoxins Test 85. MICROBIAL ENUMERATION CONSIDERATIONS The objective of a microbiological monitoring program of the water system is to provide sufficient information to control and evaluate the microbiological quality of the water produced. Product quality requirements should dictate water quality specifications. An adequate level of control can be maintained using data trend techniques and, if necessary, limiting specific microorganisms contraindicated. Consequently, it may not be necessary to detect all species of micro-organisms present in a given sample. The monitoring programme and methodology shall indicate adverse trends and detect microorganisms potentially harmful to the finished product, process or consumer. The final selection of method variables should be based on the individual requirements of the system being monitored. It should be recognized that there is not a single method capable of detecting all potential microbial contaminants of a water system. The methods used for microbial monitoring should be able to isolate the numbers and types of organisms that were considered significant in relation to the control of the system in and the impact of the product for each individual system. Several criteria should be considered when selecting a method to monitor the microbial content of a pharmaceutical water system. These These method sensitivity, variety of recovered organisms or species types, sample processing throughput, incubation period, cost and methodological complexity. An alternative consideration to the use of classical culture approaches is a sophisticated instrumental or rapid testing method that can produce more timely results. However, care should be exercised in selecting an alternative approach to ensure that it has sensitivity and correlation with classical culture approaches, which are generally considered the accepted standards for microbial enumeration. The punctuality of microbial enumeration tests after sample collection should also be considered. The number of detectable plankton bacteria in a sample collected in a scrupulously clean sample container will usually fall over time. Plankton bacteria within the sample will tend to die or irreparably adsorb to the walls of the container reducing the number of viable plankton bacteria that can be removed from the sample for testing. The opposite effect can also occur if the sample container is not scrupulously clean and contains a low concentration of some microbial nutrient that could promote microbial growth within the sample container. Because the number of recoverable bacteria in a sample can change positively or negatively over time after sample collection, it is best to test the samples as soon as possible after collection. If it is not possible to test the sample within about 2 hours after collection, the sample should be kept at refrigerated temperatures (2 to 8) for a maximum of about 12 hours to maintain the microbial attributes until analysis. In situations where not even this is possible (such as when using off-site contract labs), testing of these refrigerated samples should be performed within 48 hours of sample collection. In the delayed testing scenario, the recovered microbial levels may not be the same as those that would have been recovered if the tests had been performed shortly after sample collection. Therefore, studies should be conducted to determine the existence and acceptability of possible microbial enumeration aberrations caused by prolonged delays in testing. The classical culture approach to classical culture approaches to microbial water testing include, but are not limited to spill plates, spread plates, membrane filtration and most likely number testing (MPN). These methods are generally easy to perform, are less expensive, and provide excellent sample processing throughput. The sensitivity of the method can be increased through the use of larger sample sizes. This strategy is used in the membrane filtration method. Cultural approaches are also defined by the type of medium used in combination with incubation temperature and duration. This combination should be according to the monitoring needs presented by a specific water system, as well as its ability to recover microorganisms of interest: those that could have a effect on the product or process of use, as well as those that reflect the microbial control status of the system. There are two basic forms of media available for traditional microbiological analysis: high nutrient and low nutrient. High nutrient media, such as plaque counting agar (TGYA) and m-HPC agar (former m-SPC agar), are intended as general media for the isolation and enumeration of heterotrophic or copiotrophic bacteria. Low nutrient media such as R2A agar and NWRI agar (HPCA), can be beneficial for isolating slow-growing bacteria and oligotrophic bacteria that require lower levels of nutrients to grow optimally. Often some facultative oligotrophic bacteria are able to grow in high media nutrients and some facultative copyiotrophic bacteria are able to grow in low nutrient media, but this overlap is not complete. Low nutrient and high nutrient cultural approaches can be used simultaneously, especially during the validation of a water system as well as periodically thereafter. This simultaneous test could determine whether any additional numbers or types of bacteria can be recovered preferably by one of the approaches. In this case, the impact of these additional isolates on system control and final water use could be evaluated. In addition, the effectiveness of system controls and the hygiene of these additional isolates could be evaluated. Incubation duration and temperature are also critical aspects of a microbiological test method. Classical methodologies that use high nutrient media are typically incubated between 30 and 35 for 48 to 72 hours. Because of the flora in certain water systems, incubation at lower temperatures (e.g., 20 to 25) for longer periods (e.g., 5 to 7 days) can recover higher microbial counts when compared to classical methods. Low nutrient media is designed for these longer low temperature and incubation conditions (sometimes up to 14 days to maximize the recovery of very slow-growing oligotrophes or sanitising injured microorganisms), but even high nutrient media can sometimes increase your recovery with these longer and colder incubation conditions. Whether or not a given system needs to be monitored using high or low nutrient media with higher or lower incubation temperatures or shorter or longer incubation times should be determined during or before system validation and periodically reassessed as the microbial flora of a new water system gradually establishs a stable state in relation to its routine maintenance and hygiene procedures. The establishment of a stable state can take months or even years and may be disturbed by a change in usage patterns, a change in maintenance procedures or prevention, and frequencies, or any type of system intrusion, such as for component replacement, removal or addition. The decision to use longer incubation periods should be made after balancing the need for timely information and the type of corrective actions required when a level of alert or action is is with the ability to recover the micro-organisms of interest. The advantages gained from incubation for longer times, i.e. the recovery of injured microorganisms, slow producers or more demanding micro-organisms, should be balanced against the need for timely investigation and corrective action, as well as the ability of such micro-organisms to adversely affect products or processes. In no case, however, incubation from 30 to 35 should be less than 48 hours or less than 96 hours at 20 to 25. Typically, microorganisms that can thrive in extreme environments are best grown in the laboratory using conditions that simulate the extreme environments from which they have been taken. Therefore, thermophilic bacteria may exist in the extreme environment of hot pharmaceutical water systems, and if so, they could only be recovered and grown in the laboratory if similar thermal conditions were provided. Thermophilic aquatic microorganisms exist in nature, but usually derive their energy for the growth of the use of energy from sunlight, oxidation/reduction reactions of elements such as sulfur or iron, or indirectly from other microorganisms that derive their energy from these processes. Such chemical/nutritional conditions do not exist in high purity water systems, whether ambient or hot. Therefore, it is generally considered useless to look for thermophiles of hot pharmaceutical water systems due to their inability to grow there. Microorganisms that inhabit hot systems tend to be found in much colder locations within these systems, for example, inside point-of-use heat exchangers or transfer hoses. If this occurs, the types of recovered microorganisms are usually of the same types that can be expected from ambient water systems. Therefore, the conditions of mesophilic microbial cultivation described later in this chapter are generally suitable for their recovery. Instrumental approaches Examples of instrumental approaches include microscopic visual counting techniques (e.g., epifluorescence and immunofluorescence) and similar automated laser scanning approaches and radiometric, impedometric, and biochemically based methodologies. All of these methods have a variety of advantages and disadvantages. The advantages can be its accuracy and accuracy or its speed of availability of test results compared to the classical cultural approach. In general, instrument approaches often have a shorter lead time for achieving results, which could facilitate timely control of the system. This advantage, however, is often counterbalanced by limited sample processing yield due to extended sample collection time, costly and/or labor-intensive sample processing, or other instrument limitations and In addition, instrumental approaches are typically destructive, preventing subsequent manipulation of the isolate for characterization purposes. Generally, some form of characterization of microbial insulation, if not complete complete can be a necessary element of water system monitoring. Consequently, cultivation approaches have traditionally been preferred rather than instrumental approaches because they offer a balance of desirable test attributes and post-test capabilities. The following general methods were originally derived from Standard Methods for The Examination of Water and Wastewater, 17th Edition, American Public Health Association, Washington, DC 20005. Although this publication has undergone several revisions since its first citation in this chapter, the methods are still considered adequate to establish trends in the number of colony-forming units observed in routine microbiological monitoring of pharmaceutical waters. It is recognized, however, that other combinations of media and incubation time and temperature may occasionally or even consistently result in a greater number of colony-forming units being observed and/or different species being recovered. The prolonged incubation periods that are usually required by some of the alternative methods available offer disadvantages that can overcome the advantages of the higher counts that can be obtained. Slightly higher baseline counts that could be observed using alternative cultural conditions would not necessarily be more useful in detecting a tour or trend. In addition, some alternative cultural conditions using low nutrient media tend to lead to the development of microbial colonies that are much less differentiated in colonial appearance, an attribute that microbiologists rely on when selecting representative microbial types for later characterization. It is also ironic that the nature of some of the slow producers and the long incubation times required for their development in visible colonies can also lead these colonies to be largely unviable, which limits their additional characterization and prevents their subculture and identification. Methodologies that can be suggested as generally satisfactory for monitoring pharmaceutical water systems are as follows. However, it should be noted that these are not referee methods, nor are they necessarily ideal for the recovery of microorganisms from all water systems. Users should determine through experimentation with various approaches which methodologies are best for monitoring their water systems for in-process quality control and control purposes, as well as to recover any contraindicated species they may have specified. Drinking water: SPILL PLATE METHOD OR MEMBRANE FILTRATION METHOD1 Sample volume — 1.0 mL minimum2 Medium growth — Plate count Agar3 Incubation time — 48 to 72 hours minimum Inubam temperature — 30 to 35 Purified water: SPILL PLATE OR MEMBRANE FILTRATION METHOD1 Sample volume — 1.0 minimum2 Average growth - Plate count Agar3 Incubation time — 48 to 72 hours minimum Inubaon temperature - 30 to 35 Injection water: MEMBRANE FILTRATION METHOD1 Sample volume - 100 mL minimum2 Medium growth - Plate count Agar3 Incubation time - 48 to 72 72 minimum incitement temperature — 30C to 35C 1 A membrane filter with a rating of 0.45 µm is generally considered preferable, although the cell width of some of the bacteria in the sample may be narrower than that. The efficiency of the filtering process still allows the retention of a very high percentage of these smaller cells and is suitable for this application. Filters with smaller classifications can be used if desired, but for a variety of reasons the ability of retained cells to develop into visible colonies can be compromised, so the accuracy of the count should be verified by a reference approach. 2 When the colony count is low to undetectable using the indicated minimum sample volume,

it is generally recognized that a larger sample volume should be tested in order to obtain greater assurance that the resulting colony count is more statistically representative. The sample volume to be considered depends on the user's need to know (which is related to the established alert and action levels and the microbial control capabilities of the water system) and the statistical reliability of the resulting colony count. To test a larger sample volume, you may need to change test techniques, for example, by switching from a spill plate to a membrane filtration approach. However, in a very low to zero count scenario, a maximum sample volume of about 250 to 300 mL is generally considered a reasonable balance of sample collection and processing and greater statistical reliability. However, when sample volumes larger than about 2 mL are required, they can only be processed using the membrane filtration method. 3 Also known as Standard Methods Plate Count Agar, or TGYA Methods, this medium contains tryptone (pancreatic digestion of casein), glucose extract and yeast. IDENTIFICATION OF MICROORGANISMS Identifying isolates recovered from water monitoring methods may be important in cases where specific microorganisms transported by water can be harmful to the products or processes in which water is used. Microorganism information like this can also be useful when identifying the source of microbial contamination in a product or process. Often a limited group of microorganisms is routinely recovered from a water system. After repeated recovery and characterization, an experienced microbiologist may become proficient in its identification based on only a few recognizable traits, such as colonial morphology and staining characteristics. This may allow for a reduction in the number of IDs for representative colony types, or, with the proper qualification of analysts, may even allow shortcut tests to be done for these microbial identifications. ALERT LEVELS AND ACTION AND SPECIFICATIONS Although the use Alert and action levels are most often associated with microbial data, they can be associated with any attribute. In pharmaceutical water systems, almost all quality attributes, in addition to microbial quality, can be very quickly with almost real-time results. This short-term data can provide immediate feedback on system performance, serving as continuous process control indicators. However, because some attributes may not be continuously monitored or have a long delay in data availability (such as microbial monitoring data), properly established Alert and Action Levels may serve as an early warning or indication of a potentially approximate quality change occurring between or in the next periodic monitoring. In a validated water system, process controls should produce relatively constant values and more than adequate for these monitored attributes, so that their Alert and Action Levels are infrequently addressed. As process control indicators, alert and action levels are designed to allow corrective actions to occur that will prevent a system from completely departing from control and producing water unfit for its intended use. This minimum quality of intended use is sometimes referred to as a specification or limit. In the opening paragraphs of this chapter, the logic was presented so that microbial specifications are not included in the body of bulk water monographs (Purified water and water for injection). This does not mean that the user should not have microbial specifications for these waters. On the contrary, in most situations such specifications must be established by the user. The microbial specification should reflect the maximum microbial level in which water is still suitable for use without compromising the quality needs of the process or product where water is used. Because water from a given system can have many uses, the stricter uses should be used to establish this specification. If so, a microbial specification can be qualitative as well as quantitative. In other words, the number of total microorganisms can be as important as the number of a specific microorganism or even the absence of a specific microorganism. Microorganisms known to be problematic may include opportunistic or clear pathogens, undetected non-patetic indicators, or microorganisms known to compromise a process or product, such as being resistant to a preservative or capable of proliferating or degrading a product. These microorganisms comprise an often ill-defined group called objectionable microorganisms. As objectionable is a term related to the use of water, the list of microorganisms in such a group should be adapted to these species with the potential to be present and problematic. Their negative impact is most often demonstrated when they are present in high numbers, but depending on the species, a permitted level may exist, below which they may not be considered objectionable. As stated above, alert and action levels for a Process control attributes are used to help maintain control of the system and avoid exceeding the pass/failure specification for that attribute. Alert and action levels can be both qualitative. They may involve total microbial count levels or recoveries of specific microorganisms. Alert levels are events or levels that, when they occur or are exceeded, indicate that a process may have moved away from its normal operating condition. Alert level tours are a warning and do not necessarily require corrective action. However, alert level excursions usually lead to the alert of personnel involved in the operation of the water system as well as qa. Alert-level excursions can also lead to additional monitoring with more intense scrutiny of the resulting data and neighbors, as well as other process indicators. Action levels are events or higher levels that, when they occur or are exceeded, indicate that a process is probably adrift from its normal operating range. Examples of action-level event types include repeatedly exceeding alert levels; or in several simultaneous sites, a single occurrence higher than a higher microbial level; or individual or repeated recovery of specific objectionable micro-organisms. The excess of a level of action should lead to immediate notification of both the QA and the personnel involved in the operations of the water system so that corrective actions can be taken immediately to bring the process back to its normal operational reach. Such corrective actions should also include efforts to understand and eliminate or at least reduce the incidence of a future occurrence. A basic cause investigation may be necessary to develop an effective preventive action strategy. Depending on the nature of the action level tour, it may also be necessary to assess its impact on water uses during that time. Impact assessments may include design of affected batches and additional or more extensive product testing. It can also involve experimental product challenges. Alert and action levels should be derived from an evaluation of historical monitoring data called trend analysis. Other guidelines on approaches that can be used, ranging from surveillance to statistical evaluation of historical data have been published. The ultimate goal is to understand the normal variability of the data during what is considered a typical operating period. Trigger points or levels can then be established that will signal when future data may be approaching (alert level) or exceeding (action level) the limits of this normal variability. Such alert and action levels are based on the control capacity of the system because it was being maintained and controlled during this typical control history period. In new water systems where there is very limited or non-limited historical data to derive data trends, it is common to simply establish initial levels of alertness and action based on a combination of resources equipment design, but below the process and product specifications where water is used. It is also common, especially for ambient water systems, to mature microbiologically throughout the first year of use. Pelo Pelo of this period, a relatively stable state microbial population (types and levels of microorganism) will have been allowed or promoted to develop as a result of the collective effects of routine system maintenance and operation, including the frequency of unit operation reengagements, backwashings, regenerations and hygiene. This microbial population will usually be larger than when the water system was new, so it should be expected that data trends (and the resulting alert and action levels) will increase during this maturation period and eventually level. A water system should be designed so that performance-based alert and action levels are well below water specifications. With poorly designed or maintained water systems, the system owner may find that the system's initial microbial levels were acceptable for water uses and specifications, but mature levels are not. This is a serious situation, which if not correctable with maintenance and hygiene of the system more frequent, may require an expensive reform of the water system or even replacement. Therefore, it cannot be overemphasized that water systems should be designed to facilitate microbial control, so that when monitored against alert and action levels, and maintained accordingly, the water continuously meets all applicable specifications. An action level should not be established at a level equivalent to the specification. This leaves no room for corrective system maintenance that could avoid a specification tour. Exceeding a specification is a much more serious event than an action-level tour. A specification tour can trigger an extensive investigation of the impact of the final product, substantial corrective actions within the water system that may include a complete shutdown and possibly even product rejection. Another scenario to avoid is the establishment of an arbitrarily high and generally performance-based level of action. Such unrealistic levels of action deprive users of significant values of indicators that could trigger the maintenance of the corrective system. Unrealistically high action levels allow systems to grow well out of control before actions are taken, when their intention must be to pick up a system imbalance before it gets wildly out of control. Because alert and action levels should be based on actual system performance, and system performance data is generated by a given test method, it follows that these alert and action levels should be valid only for test results generated by the same test method. It is invalid to apply alert criteria and action level to test the results generated by a different test method. The two test methods may not recover microorganisms equivalently same water samples. Similarly, invalid is the use of trend data to derive alert and action levels for a water system, but applying these alert and action levels to a different water system. Alert and action levels are specific to the water system and test method. However, there are maximum microbial levels above which action levels should never be established. Water systems with these levels should be unquestionably considered out of control. Using the microbial enumeration methodologies suggested above, generally considered maximum levels of action are 100 cfu per mL for purified water and 10 cfu per 100 mL for water for injection. However, if a given water system controls microorganisms much more tightly than these levels, appropriate alert and action levels must be established from these tighter control levels so that they can actually indicate when water systems may be starting to get out of control. These microbial control parameters in process should be established well below the user-defined microbial specifications that outline the fitness of water for use. Special consideration is required to establish the maximum levels of microbial action for drinking water, as water is often delivered to the facility in a condition over which the user has little control. High microbial levels in Drinking Water may be indicative of a disturbed municipal water system, main broken water or inadequate disinfection, and therefore potential contamination with objectionable microorganisms. Using the suggested microbial enumeration methodology, a maximum level of reasonable action for drinking water is 500 cfu per mL. Considering the potential concern with objectionable microorganisms raised by such high microbial levels in the feeding water, informing the municipality about the problem so that they can initiate corrective actions should be an immediate first step. Internal corrective actions may or may not be necessary, but may include additional coliform testing in the incoming water and pretreatment of water with additional chlorination or irradiation or filtration of UV light or a combination of approaches. Approaches.