

# PHARMACEUTICALS

## PRACTICAL MICROBIAL CONTROL TECHNIQUES FOR PHARMACEUTICAL WATER PURIFICATION SYSTEMS

**A**ttentive control of bacteria throughout a pharmaceutical water generation system is critical to maintaining desired microbial levels at the system outlet, throughout generation, storage and distribution, and at points-of-use. This article will discuss the current practical techniques to manage, remove, and reduce bacteria, consisting of temperature, hydraulics, sanitizing agents, membranes, sub-micron filters, and ultraviolet (UV) lights. The benefits of systems with the ability to be completely hot water sanitized will be examined, as well as overall design strategies to ensure proper system operation. Effect on system process design, maintenance, and system operation will be reviewed.

### Microbial Control

As with the production process for any drug product or component, pharmaceutical water production, storage, and conveyance systems are validated because end-product testing alone is not sufficient evidence to confirm, with a high degree of assurance, that the system operates as it is purported. During the performance qualification (PQ) phase of validation, sanitization frequencies are established based on the acceptable microbial limits throughout the system, not exclusively at the use-points. Sanitization and maintenance intervals may be predicted prior to the PQ, but they are ultimately finalized and verified based on system operation.

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Validation of pharmaceutical water production is atypical in that there are no replicate process runs required or validation of worst-case challenges to the system. However, due to the dynamic nature of the process (i.e., varying feedwater bacteria levels), detailed examination is critical. This process must be considered as an enduring process validation exercise that is unique to every pharmaceutical water system. The monitoring and analysis of microbial (and microbial control) data are often the most challenging of all control parameters. The regulated chemical parameters for pharmaceutical waters are much easier to detect and analyze, and excursions are more readily predicted, rationalized, and resolved.

The pharmaceutical industry accepted maximum microbial Action Levels for Purified Water and Water for Injection (WFI) are 100 colony forming units per milliliter (cfu/mL) and 10 cfu/100 mL, respectively. The levels are reinforced by an U.S. Food and Drug Administration (FDA) Guide for Inspection that states: "agency policy, is that less than 10 cfu/100 mL is an acceptable action limit [for WFI]", and "any action limit over 100 cfu/mL for Purified Water is unacceptable" (1). In addition, although these levels are considered industry standard, there is certainly no established procedure regarding the culturing techniques for microbial testing. Variances among different culturing techniques for enumeration of viable bacteria in pharmaceutical water systems is expected and has been well documented. However, all of the perplexity regarding permissive microbial levels is often inconsequential. It is common for Action and Alert Levels for compendial waters to be established well below these limits because of product-specific requirements or desired product attributes.

Further ambiguity centers on the acceptable microbial levels not at points-of-use, but throughout the generation system. For compendial waters, feedwater must comply with U.S. Environmental Protection Agency (EPA) National Primary Drinking Water Regula-

tions only. However, these standards have no direct established limit for total viable bacteria. To date, the United States Pharmacopoeia (USP) has set a recommended action limit for drinking water of 500 cfu/mL. Even though, a majority of domestic feedwater sources would never experience bacteria levels approaching 500 cfu/mL because they are often subject to additional standards for potable waters and treated by municipal water systems that would include the addition of a disinfection agent. It is recognized that the storage and distribution system should not be considered "polishing" techniques to control bacteria and that the same Alert and Action Levels established at points-of-use should be stipulated for the outlet of the generation system.

So, what are appropriate maximum action levels for bacteria throughout a pharmaceutical water generation system? There are those that reason that if 500 cfu/mL is the accepted maximum limit for bacteria at the inlet of a system, that this same limit should not be exceeded anywhere throughout the process train. Although apparently logical, this limit becomes more difficult (and sometimes impossible) to maintain in the absence of a residual disinfectant and in concentrated streams (such as reverse osmosis concentrate), many of which are recycled to achieve sensible water conservation. Yet, to establish unreasonably high microbial limits throughout the system would not be defensible. The FDA has not published recommended microbial levels for intermediate points in the water generation system.

A logical microbial program should be established based on operating the system within a "state of control". Intra-component monitoring and trending of bacteria levels is critical to not only establishing sanitization and maintenance intervals, but predicting system upsets and product contamination before they occur; the very essence of process validation. To achieve this "state of control", there is not one design aspect or process that is exclusively employed. For example, relying exclusive-

ly on a terminal filtration for bacterial reduction, while simultaneously neglecting bacterial control throughout the system, would not be acceptable. Mechanical design features and additional unit operations should be included only when the expected benefit (e.g., reduced maintenance, less downtime) is realized at an acceptable cost. As the most common alternatives for microbial control of pharmaceutical water systems are discussed below, the difficulty in predicting actual performance due to independent system variables, including unique source water qualities, should not be lost.

### **Mechanical Design**

Operation of pharmaceutical water treatment systems can impact the final pharmaceutical product and therefore must comply with the current Good Manufacturing Practices (cGMPs) for Finished Pharmaceuticals, 21 CFR Part 210–211. Although not written specifically for water systems, some concepts are easily extended to water systems, but relatively little information could extend specific design attributes of these systems. Instead, many mechanical design concepts are adopted from industry standards for sanitary design (2). Naturally, product contact surfaces such as water storage and distribution systems are typically designed to a particular sanitary standard, whereas not all generation processes and unit operations are. Likewise, WFI systems, which inherently require lower microbial counts than Purified Water systems, frequently possess mechanical features that are more elaborate.

Sanitary systems for pharmaceutical waters imply the use of smooth surfaces with minimal connections. Connection points should again be smooth and have minimal space to harbor bacteria. All materials in sanitary systems should contain minimal leachates, have excellent corrosion properties, and have the ability to be cleaned and sanitized without difficulty. The ASME Guide for Biotech Processing Equipment (3) defines sanitary as “of or pertaining to equipment and piping systems that by design, materials of construction, and operation provide for the maintenance of cleanliness so that products produced by these systems will not adversely affect human or animal health”.

Of note is that this definition is not only for piping systems, but also the equipment itself. Most unit operations found

in water treatment systems would not be considered sanitary by any definition. Certainly, the source water, often potable water from a municipality, would not be delivered by a sanitary piping system. Processes such as filtration media beds, reverse osmosis (RO) membranes and ion-exchange (IX) beds, and continuous electrodeionization (CEDI) modules are not truly sanitary in that smooth surfaces and minimal crevices do not exist, and the cleanliness is only gauged by validation of the sanitization process for this equipment.

The benefit of having sanitary piping system for a less than sanitary unit operation could be debated. Yet, the ability to mechanically design the process to hygienic standards to the greatest extent possible would be desirable to minimize the frequency of sanitization. Sanitary design and construction of all water system components is often not financially practical even when it is technically feasible.

Pretreatment components such as media filters, ion-exchange softeners, and cartridge filtration can be operated with the presence of a residual disinfectant such as chlorine or chloramine. Sanitary components at this point in the system, when a residual disinfectant is present, are not essential to proper operation. However, RO and IX systems generally require the absence of residual disinfectants, and therefore control of bacterial growth becomes more critical. Thus, one could argue that it would be appropriate to consider a sanitary design upon removal of the residual disinfectant.

A second contention would be that sanitary components are suitable at the point in the system where low bacteria counts are expected. For an RO-based system, sanitary design would typically be established downstream of the RO membranes with the low-pressure permeate piping where low bacteria counts would be anticipated. Further, the *ISPE Guide for Water and Steam* defines sanitary design as “a system of design that meets standard, specification, codes, regulatory and industrial guidelines, and applicable engineering design methods to reach a degree of sanitation required by food, pharmaceutical, and cosmetics processing” (4).

The velocity of water, to induce turbulence, through piping systems has historically been considered an important design parameter. As applied, design velocities should not be considered as

critical for pharmaceutical water purification generation systems as distribution systems, especially in the chlorinated portions of those systems. Minimum velocities, required for minimization of biofilm formation and development, have been suggested for non-chlorinated systems based on both research (5) and practical application (6). A minimum design velocity of 2 to 3 feet/second (ft/sec) is generally regarded as industry standard, with a target velocity between 5 to 8 ft/sec.

While it is logical to suggest that water velocities should be as high as possible, pressure losses at velocities greater than 8 ft/sec generally limit the use of smaller pipe sizes. In addition, target velocities are not always obtainable because systems will operate at variable flowrates for each process such as normal operation, recirculation, cleaning (including backwash and regeneration steps), and sanitization. The inability to meet one design velocity has also been discussed for pharmaceutical water distribution systems (7).

While design velocities should certainly be considered for generation systems, it is not critical that minimum and maximum velocity requirements are met during all phases of system operation. No level of velocity or turbulence can totally inhibit microbial growth. Regardless of the minimum velocity requirement, some flow (or periodic flushing) is always preferred to a stagnant system. This would include the use of spray balls on process tanks to ensure that there are no stagnant areas in head spaces above water levels. Installed spare pumps should be periodically operated or isolated from the system entirely, most commonly by the use of swing elbow piping arrangements.

The focus on materials of construction and roughness of piping surfaces obviously becomes more critical when lower microbial counts are expected. In chlorinated streams, where microbial problems are seldom encountered, the surface finish of the piping systems is not considered a critical design parameter. Plastic piping, such as polyvinyl chloride (PVC) or acrylonitrile-butadiene-styrene (ABS), or mill-finish steels are generally acceptable. For non-chlorinated streams or certainly for sanitary process streams, piping and material finishes are more closely scrutinized. In Purified Water and WFI Systems, 316L stainless steels with finishes of 25 $\mu$ -inch roughness average (RA) and 15 RA are com-

mon (4). Plastic piping systems such as polypropylene and polyvinylidene fluoride (PVDF) are also used, especially in certain biotechnology applications. Surface smoothness for these plastic systems can exceed even electropolished stainless steel systems (8).

Biofilm formation is affected by the surface topography and chemistry of the piping system that varies for different materials of construction (9). Surface finish is not the only design parameter, and may be not the most important, to controlling bacteria and biofilm development. Typically, surface finish requirements are mandated for sanitary pharmaceutical water piping systems.

The current Good Manufacturing Processes for Large Volume Parenterals (cGMPs for LVPs) (21CFR Part 212) had contained more engineering and design details specific to pharmaceutical water systems. Since abandoned, nothing outlined in Part 212 is considered a legal requirement. However, many of the proposed concepts are considered to be Good Engineering Practice, particularly for sanitary water treatment systems, and thus are considered cGMP. These practices include contamination and microbial control techniques such as double tube sheet shell and tube heat exchangers hydrophobic vent filters for sanitary systems.

One additional design objective, outlined in Part 212, is the ability of a piping system to be sloped to drain and the entire system to be completely drainable. In the context of Part 212, the intent of a fully drainable system was to facilitate the draining of condensate after a system had been steam sterilized. The complete drain ability of ambient or chemically sanitized piping systems that do not have the ability to be steamed is not required. Nor is it reasonable for many water treatment unit operations, many of which do not have the ability to be steamed, to be required to be drained completely free of water.

Processes such as IX resins, membranes and filtration media naturally absorb water and the addition of extensive desiccation systems would be impractical. The ISPE Baseline Guide for Water and Steam Systems offers a concurring statement: "Systems that will never be steam sterilized do not need to be fully drainable, as long as water is not allowed to stagnate in the system". In fact, make-up treatment systems as well as distribution piping networks that are drained and not completely dehydrat-

ed, are likely more susceptible to microbial growth than systems that recirculate under a controlled environment. Introduction of a preservative or antimicrobial agent into the system would better partial drainage of many unit operations during extended periods of inoperability. Thus, for equipment and piping systems that will never be steamed, the incorporation of sloped piping, low point drains, and high point vents offers no microbial control advantage and should not be considered, unless drainability is required for other purposes.

Dead legs in sanitary piping systems are defined as an area of piping, generally associated with an instrument sample valve connection point, where the branch section of piping exceeds a defined length. The FDA Guide to Inspection of Water Systems had defined a deadleg as a length of piping greater than six times the diameter of the branch piping when measured from the centerline of the main piping run (1). For larger piping networks, especially with small branch connections, it becomes increasingly difficult or at times impossible to meet this requirement.

A recent definition (4), suggested that a deadleg be defined based on the distance from the main piping wall rather than the centerline to the end of the deadleg. According to this definition, current industry practice is to attempt to minimize deadlegs to less than 4D (where D is again based on the branch pipe diameter). Regardless of the definition of a deadleg, stagnant areas should be minimized wherever possible in both sanitary and non-sanitary systems. For sanitary systems short bull tees for instrument connections and prefabricated valves with minimal, if any, deadleg are commonly employed. However, in non-sanitary systems, which may include non-sanitary piping systems, the 4D or 6D requirement should not be considered an absolute requirement.

A "sanitary" system that contains no polishing of stainless piping may not show a quantifiable difference in operation from an identical stainless system with a high degree of surface finish. However, if the same "sanitary" system was also designed to operate at a very low velocity, with stagnant areas, deadlegs, and threaded piping connections, the sanitary portion of the system would be much more susceptible to microbial problems. If a "more hygienic" design

could be implemented at a reasonable cost, regardless of the location in the process train or type of system (sanitary versus non-sanitary), then the design should be considered. When the mechanical design is compromised, the risk of microbial upsets, beyond a state of control, is increased. This would increase the sanitization frequency required to maintain operation with the established Alert Levels.

### Process Design

One of the most important, and often overlooked, design parameters is the system operating temperature. System operation below 20 °C or above 65 °C can prove to be an excellent mechanism to help control bacteria throughout the system. Elevated temperature operation would only appear to be economically justified where elevated temperature water is required for the process. Further, the number of unit operations capable of continuous operation at elevated temperatures is limited. Operation of generation systems at reduced temperatures may be a practical alternative. A far greater number of pharmaceutical water generation systems prone to microbial tribulations have been found in warmer climates that do not have any feedwater temperature control (2).

Table A shows data generated from a pretreatment generation system in operation with and without temperature control over two separate two-week periods. The system operated with continuously lower microbial counts throughout the pretreatment system and required less frequent sanitization of the RO and deionization (DI) systems when the operating temperatures was not allowed to exceed 20 °C. The ability to temper the incoming feedwater to 10 °C to 20 °C in an attempt to control microbial activity will depend on the availability and cost of a chilled medium, additional microbial control techniques in the system, and the nature of the feedwater source.

As it is not mandatory that the feedwater source to a pharmaceutical water system contain a residual disinfectant level, a monitoring program should be established for feedwater disinfectant level. It may be necessary, when no or little disinfectant (typically chlorine or chlorine-based compounds such as chloramines) is present, to supplement the system with injection of sodium hypochlorite. Even when the feedwater is chlorinated, bacteria may still be present,

possibly attached to particulate material in the feedwater stream (10) or present in an inactive state (11).

Although it would be unlikely to experience unacceptable viable bacteria in portions of the generation system where disinfectant is present, proliferation of microorganisms in packed beds and columns has been experienced in many systems. These outbreaks are generally found in warmer feedwaters with high organic concentrations. Once established, bacterial colonization in pretreatment columns, either as an established biofilm on the vessels and piping or throughout the bed, can be very difficult to remove. Chemical sanitization of sand and media filters, water softeners, granular activated carbon beds, and other packed columns that are not designed to accommodate hot water or steam is a very difficult and time consuming process whose results are not always successful.

The best method to prevent excess microbial growth in pretreatment systems is to ensure adequate concentrations of residual chlorine are present. Chlorine concentrations greater than 0.2 milligrams per liter (mg/L) are generally sufficient if present in the incoming feedwater. This concentration should be met throughout the pretreatment system up to the point of removal. One should always consider recirculation streams (especially concentrate recirculation streams, and any periods of complete system recirculation to ensure that the concentration of chlorine is not diminished or absent altogether. Supplemental injection via on-line monitoring of the chlorine concentration may be required up to concentrations of 1.0 mg/L since contact time for the chlorine in the system will be minimal. Generally, the maintenance of a minimum chlorine residual is a practical technique that is relatively easy and inexpensive to provide.

Reverse osmosis, CEDI, regenerable DI, and distillation are the most common DI processes currently used to generate pharmaceutical waters. Disregarding distillation, which is normally operated at elevated temperatures, membrane and IX systems are not inherently sanitary processes. The ability to provide a degree of cleanliness for these systems is frequently a concern of the pharmaceutical water industry.

The advancement of RO membranes that do not employ brine seals is one example. These elements allow for a

regulated bypass flow of water between the membrane element and the pressure vessel, thus minimizing possible stagnant areas. This exemplifies a relatively inexpensive method of reducing the risk of major microbial problems. Recirculation of reject or waste streams, necessary at times to maintain proper system hydraulics in RO systems at reasonable water recoveries, can have detrimental affect on RO performance and cleaning frequency. These reject stream will be concentrated with both bacteria and nutrients. When these streams are recovered, it is preferable to return these stream upstream to the chlorinated portion of the system, supplementing the system with additional disinfectant as required.

For IX-based systems, the operation of the system can play an important role in controlling bacteria. Deionization systems downstream of RO units will be less susceptible to biological contamination because of the reduced biological and organic levels downstream of membranes. For regenerable DI-based systems, additional prevention is provided by the chemical regeneration of the resin with acid and caustic. The regeneration process can serve as a self-sanitization and minimize the requirement for a separate sanitization step or process.

Separate cation and anion columns have a propensity to operate with lower total viable bacteria levels in the effluent compared to mixed-bed DI because of the pH fluctuations from the first to second beds. Additional microbial control can be realized by not allowing the system to remain stagnant for extend periods. For generation systems that would not be required to produce water continuously, it would be preferred to have the system continuously recirculate or periodically flush. Either of these two methods to minimize stagnation has been used successfully and both generally require a portion of the water to drain.

Continuous recirculation of all process and waste streams in the generation system is usually not desirable. A portion of the water should be discharged and the system replenished to prevent the system temperature from elevating and to allow for a portion of the volume to be blown down from the system. For systems that remain stagnant, it is recommended that a periodic system flush is performed. The benefit of rinsing the system, even for only short

intervals, is extremely effective.

Table B shows the effect of a 5-minute flush, after a stagnation period of two weeks, on a regenerable DI system. Testing for total viable bacteria at the outlet of the column showed a consistent reduction after the 5-minute rinse was performed. For all DI systems that could potentially remain idle, either a periodic rinse or continuous recirculation should be employed. For regenerable DI systems, periodic flushes may be more appropriate since continuous recirculation may elute some of the exchanged ions on the resin resulting in premature exhaustion of the IX bed. For portions of the generation system that remain chlorinated, the benefits of recirculation are highly questionable.

All of the design criteria mentioned above are examples of preventative measures to limit bacteria from accumulating and flourishing. In fact, the presence of bacteria is ubiquitous and there is no practical method for totally eliminating bacteria from pharmaceutical water systems. Therefore, it is quite acceptable to supplement an established microbial control program with techniques that actually remove or reduce bacteria from the system. Periodic sanitization would be one example of this type of technique.

Other such methods include the use of bacterial reduction (typically sub-micron) filters and ultraviolet (UV) lights. The use of UV light at 254-nanometer (nm) wavelength for microbial reduction is common in pharmaceutical water treatment systems. Most often, UV is employed just downstream of removal of residual disinfectant, if either activated carbon or sodium sulfite injection. Successful applications of UV light also include protection of membranes and resins from biological fouling, or as a final-polishing technique as the terminal step prior to storage and distribution or in a distribution or recirculation loop.

The appropriateness of sub-micron filtration as a final polishing technique has been the subject of increasing debate in recent years. In general, sub-micron filters would only be applicable as a terminal processing step or as a polishing technique in a recirculation loop. For WFI, implementation for these applications is prohibited. Although their use in Purified Water and non-compendial generation and distribution systems may illicit a more scrutinized investigation by regulatory personnel, their use is not forbidden. It is impera-

**TABLE A**  
**Data from a Pretreatment Generation System**  
**with and without Temperature Control**

<i>Sample Location</i>	<i>Total Viable Bacteria Range (cfu/mL)</i> (5-20 °C operation)	<i>Total Viable Bacteria Range (cfu/mL)</i> (5-30 °C operation)
Media filter effluent	15-180	10-200
Activated carbon unit effluent	1,500 - TNTC	30-370
UV unit effluent	800 - TNTC	<1-125
Water softener effluent	1,200 - TNTC	15-280

**TABLE B**  
**Effect of a 5-Minutes Flush**  
**after a Stagnation Period of Two Weeks**

<i>Type of System</i>	<i>Total Viable Bacteria in Effluent (cfu/mL)</i> (prior to flush)	<i>Total Viable Bacteria in Effluent (cfu/mL)</i> (after flush)
Mixed-bed DI system	180	18
Mixed bed DI system	TNTC	3
Mixed bed DI system	178	8
Mixed bed DI system	65	3
Activated carbon unit	35	24
Activated carbon unit	96	4
Activated carbon unit	300	28
Activated carbon unit	210	37

tive that the use of sub-micron filters, as a tool for microbial control, be only one component of a complete microbial strategy for the system and that a proper validated preventative maintenance program is established that includes periodic integrity testing. Both UV lights and sub-micron filters are practical techniques for many pharmaceutical water treatment systems.

### Sanitization

An overall sanitization strategy is essential to successful system operation. It is imperative that every unit operation of a pharmaceutical water purification system has the ability to be properly and effectively sanitized. The three most common methods of equipment sanitization are chemicals, heat, or ozone. Of the three, only chemicals and heat would be practical for most unit operations. Chemical sanitization would ideally occur after a chemical cleaning of the operation, such as with RO or CEDI. Chemical sanitization of IX columns would be appropriate, if required, after regeneration (a subsequent regeneration would again be required after chemical sanitization). In general, chemical sanitization is a manual process. The

sanitization is validated by testing to ensure the proper concentration of sanitant is present throughout the system, ensuring that it has been sufficiently displaced, and microbial sampling before and after operation.

Hot water sanitization has historically been limited to carbon beds, certain filters, and distribution systems. Thermal sanitization has now been extended on a commercial basis to RO membranes and CEDI modules. The ability to hot water sanitize RO systems (as well as DI and CEDI systems) could be available with only a minimal impact on the capital cost if the system is designed on stainless steel or thermally stable components (12). As the hot water sanitization process for these operations is generally automated, increased frequency with minimal additional labor requirements could be an attractive preference, especially when conservative Action Levels are required or established throughout the generation system.

### Conclusions

The details of system design can balloon the capital cost of a system with the addition of extensive attributes. The

incorporation of features, equipment, and sanitization capabilities should be evaluated based on feedwater quality, required microbial control requirements throughout the generation system, and expected maintenance. Practical microbial control and reduction techniques do not always require expensive design options for successful system operation. Indirect microbial control techniques such as fluid velocity, surface finish, and piping design are frequently required; however, it is generally necessary to employ direct microbial control methods such as temperature control, sanitization of components, residual disinfectant, sub-micron filters, and UV lights to minimize maintenance. Often the elimination of one indirect design concept may not have a dramatic effect on operation and maintenance, but a combination of mechanical design inadequacies can lead to a system that requires excessive or constant maintenance.

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