

COMPARISON OF HIGH PURITY WATER FOR MICROELECTRONIC AND BIOPHARMACEUTICAL FACILITIES

**BY ANDREW BAIRD, KIRSTEN SOMMER, P.E., AND RALPH
WILLIAMS, P.E.**

This article presents in brief the major regulatory, design, operational, and economic differences between high purity waters employed in biopharmaceutical production and in microelectronics fabrication.

INTRODUCTION

To appreciate the technical influences and possible future trends, design engineers and operators of biopharmaceutical high purity water systems may find it beneficial to compare systems for their industry with those of the microelectronics industry. Each industry has unique strengths that may be leveraged by the other industry.

Highly purified water is utilized in biopharmaceutical and microelectronics industries. The former uses high purity waters for production, processing, formulation, cleaning, and rinsing. Biopharm operators are primarily concerned with microbial, chemical, and endotoxin contaminants that may compromise standards of safety, efficacy, strength, purity, and quality of a drug. There are two commonly used grades of pharmaceutical bulk water: water for injection (WFI) and purified water (WPU). In microelectronics, high purity water is typically called ultrapure water (UPW). Microchip fabricators are concerned with particulate, ionic, and organic contamination detrimental to the integrity of microchip circuitry. The majority of UPW is used for wafer cleaning, rinsing and process equipment component cleaning.

REGULATORY ENVIRONMENT

Biopharmaceutical communities mandate their own water regulations; Europe¹, Japan², and United States³ each publish official documents listing drugs with directions for specific quality attributes. These publications are known as pharmacopoeia (derived from the Greek word *pharmakopaios*, drug maker). Pharmacopoeial standards regulate water grades, specific quality parameters and test procedures. They do not specify operating conditions or the application for each grade of water. A European draft paper gives some guidance for water quality for pharmaceutical operations⁴.

In the United States and Europe water for injection(s) (*Aqua ad iniectabilia*) and purified water (*Aqua purificata*) are known as compendial waters; e.g. minimum requirements are set forth in the current edition of Official Monographs in the United States Pharmacopoeia (USP 24) and European Pharmacopoeia Third Edition Supplement 2000. In the US, the Food and Drug Administration (FDA) enforces implementation of these regulations adopted

through the federal codification system. In Europe, the European Agency for the Evaluation of Medicinal Products (EMA) implements standards in member states code systems.

In addition to the United States Pharmacopoeia, Title 21 of US Code of Federal Regulations (CFR) Parts 210 and 211, otherwise known as current Good Manufacturing Practices⁵, provides some guidance, and the FDA Guide to Inspections of High Purity Water Systems⁶ gives information for design, and operation of compendial water systems. However the information presented in these documents is not intended to be an engineering design guide. Certain design approaches are evaluated or implied. Individual users must interpret this information and justify their design to the FDA during the validation process. Misinterpretations have led to systems not being validated or approved by the FDA. The ISPE Water and Steam Guide⁷ was developed to assist engineers in designing water systems to attain FDA compliance with out excessive design or one-upmanship engineering solutions.

For the microelectronics industry, quality parameters are discretionary by the owner and are not regulated. Each manufacturing operation develops internal quality specifications based upon processing requirements, with bench-marking to American Society for Testing and Materials (ASTM), Semiconductor Equipment and Materials International (SEMI), Balazs Labs, Sematech, and other industry sources. An example is ASTM D5127-99, Standard Guide for Ultrapure Water Used in the Electronics and Semiconductor Industry, which presents recommendations for water quality for various product types.

The requirement to design compendial water systems to attain legally enforced standards has far reaching consequences. When designing water systems, engineers and operators tend to concentrate on solutions that have a proven validatory track record. The biopharm industry is consequently slow to respond to developments in equipment and analytical innovations. A new design approach will require validation. Validation is an enhanced process of commissioning and testing by establishing documentary evidence for critical equipment and process parameters.

Validation occurs in three formal stages, installational qualification IQ, operational qualification OQ, and performance qualification PQ. Qualifications are executed according to acceptance criteria defined in individual protocols. The installational qualification demonstrates that the system has been installed in accordance with design drawings, specifications and the manufacturer's recommendations. The operational qualification demonstrates that the system or equipment operates consistently as specified, by meeting design requirements for control of operating parameters. The performance qualification demonstrates that the system or equipment performs consistently as specified by meeting process requirements and parameters under simulated production conditions. In order to evaluate the effect of seasonal variation on potable water supply, it may take at least one year to execute a performance qualification. In the race to market, manufacturers cannot afford to delay production schedules to evaluate new equipment or an innovative design. Design changes to an existing validated system must be revalidated to prove that the new

system is equivalent to the original. The impetus to change a system already providing consistently high quality water is low, despite the fact that an improvement may result in decreased operating cost or more efficient operation.

Because microelectronics firms independently develop their quality specifications and are not bound to design/construction guidelines, they are free to test various water treatment technologies and analytical approaches. This led to a great deal of water treatment innovation in the 1980s and 90s that has proved beneficial to both the microelectronics and the pharmaceutical industries. Although this innovation has slowed in recent years, microelectronics firms continue to pilot test and work with component manufacturers. This culture of technology growth, flexibility, and the lack of regulation does lead to problems: e.g., quality specifications that are unattainable and unmeasurable, comparison of performance between the systems are difficult, and there is little component and equipment standardization. Validation of a UPW system is an owner-prescribed process of commissioning and testing.

WATER QUALITY SPECIFICATIONS

The biopharm industry sets operating specifications to achieve regulatory standards rather than product requirements. Because of the complexity of biological and biochemical entities, apart from microbial concerns producers have generally devoted little attention to quality of water actually required by the process. Perhaps process performance could be enhanced with water of a quality higher than regulations. In general, users rely upon compendial standards for production method and dosage form to determine the type of water required. Operating limits are set to reduce the risk of dropping below the regulated level into noncompliance situation. Users are willing to pay for the high cost of WFI/WPU systems to consistently generate high quality water because of the risk of lost product to market, in the event of lack of compliance.

Water quality specifications for microelectronics systems tend to aim towards best-achievable and best-measurable levels of contaminant control. The strong and measurable correlation between UPW quality and product yields provides adequate incentive to pay for expensive, highly reliable, and effective water treatment systems. The UPW system for a semiconductor manufacturer is usually the most expensive utility system in a new factory.

For US pharmaceutical applications the current standard is USP 24, (previously USP 23) which eliminated individual ion and metals levels in favor of conductivity and total organic carbon (TOC) for both WFI and WPU. In addition, WFI is required to have an endotoxin level of less than 0.25 EU/ml (see Table A). The USP Monographs do not specify microbial limits. Instead water systems are monitored to confirm they operate within their design specifications and produce water of acceptable quality. Recommended appropriate action levels are described in Table A. Action levels should represent product quality concerns and the ability to effectively manage the treatment process. Conductivity and total organic

carbon (TOC) are commonly measured online, and endotoxins and bacteria are measured offline. Methods for offline and online measurement are documented by USP.

In contrast, microelectronics specifications will generally not include an endotoxin requirement, but cover resistivity, TOC, bacteria, particles, dissolved oxygen (DO), silica, anions/cations, and metals. Gross contaminants such as resistivity, TOC, particles, DO, silica, and sodium are measured online continuously, while specific contaminants such as halogens, inorganic and organic species are measured individually offline. Specifications for ionics and metals are often driven by laboratory detection levels in the 10 to 100 parts-per trillion (ppt) range. Some manufacturers will even drive specifications below the detection levels and require sample concentration for testing, although this is not yet a common practice. Analytical instruments and procedures are not regulated and can vary from site to site.

At present, particle measurement is restricted to UPW. As unobtrusive inline instrumentation becomes available and more reliable this may find integration into USP requirements. Table A show a comparison of maximum contaminant levels for various biopharmaceutical and microelectronic specifications. These specifications generally apply at the point-of-use.

OPERATIONAL AND DESIGN OBJECTIVES

Design differences between biopharmaceutical and microelectronics water systems are better understood when one considers the operational objectives of the facilities. Of primary concern to biopharmaceuticals is that the high purity water system be successfully validated, and consistently produce water compliant with USP 24. This includes the overriding need for a high quality water supply and a distribution network that can be frequently sanitized for bacterial mitigation. Typical biopharmaceutical manufacturing operations occur one- or two-shifts per day with a 5-day-work week. For microelectronics, the primary objective of the water system is to create and distribute ultrapure water on a 24 hour 365 day basis with no shutdowns, while maintaining purity. While the biopharmaceutical firm is acutely aware of the impact of lost compliance, the microelectronics firm is concerned with any reduction in product yield.

For both industries, microbial-retentive filters are rarely used at the use-point. Instead, distribution loops are designed to minimize bacterial potential by sizing piping for turbulent flow. Turbulent flow is assured by maintaining a Reynolds numbers in excess of 2,500 (a more commonly specified level is 10,000) at the end of the supply headers. The debate continues over the effectiveness of reducing microbial contamination by increasing the water velocity beyond minimum turbulent levels^{8,9}. Studies have demonstrated that raising the velocity beyond that required for minimum turbulence serves only to waste recirculated water capacity, restrict loop flexibility, and cost more to pump. In practice, when the process demands water, a requirement for turbulent flow results in supply velocities of between 3 and 5 feet per second (fps), or as limited by the piping dynamic pressure losses¹⁰.

Figure 1 highlights the overall system configurations for a WFI and a UPW system. WFI source water is fed from a continuously circulated WPU source and becomes WFI upon distillation or reverse osmosis (RO). WFI can be distributed either hot or at ambient temperatures. A UPW polish system is similarly fed from a circulated purified water source, the primary system, which is in turn fed by a pretreatment/makeup system.

CAPACITY, SCALE, AND COST

The scale of water consumption can be vastly different between the two applications; a microelectronics plant may be as small as 150,000 gallons per day, but is typically as large as 2 million gallons per day. A WFI/WPU generation system can be as small as 10,000 to 50,000 gallons per day, or as large as 1 million gallons per day (typically for WPU only). The type and number of process operations drive this wide variation in WFI/WPU system capacities. Biotech facilities consume much of this water in rinsing and washing of tanks and interconnecting piping. Pharmaceutical users require water for compounding, finishing and washing.

In spite of these size differences, the process of identifying the necessary capacity for a given biopharmaceutical or microelectronics plant is very similar:

- Determine facility average demand based on either tool load projections or based on benchmarking data.
- Size the WPU, makeup, and primary systems to support this average facility demand plus reject and maintenance flows within the water treatment system.
- Size the circulated supply loops for the average demand, with some peak demand factors plus the minimum circulation flows for turbulent flow. While a microelectronics facility with a consumption of 2 million gallons per day would have a loop circulation of 2,000 gpm, the typical WFI/WPU circulation flow would be closer to 200 gpm. There is in general an order of magnitude separation between the sizing scales for the two facility types.

Restrictions on storage of WFI/WPU are dependent upon system temperature and hold volumes. Generally a hot dynamically circulated system is considered to be self sanitizing and hold times are not an issue if in compliance. Recirculated and non-recirculated ambient systems without sanitization should be drained every 24 hours, especially if WFI. This scale difference will drive storage tank sizes for compendial waters of between 1,000 to 5,000 gallons, while UPW storage tanks sizes are limited by transport and shipping considerations; 38,000 gallons with 14-foot diameter are commonly seen. While UPW tanks used to be designed for 2 to 4 hours of storage capacity, as capacities increased, the tank sizes ran into practical size limitations.

Although capital costs of biopharmaceutical and microelectronics high purity water systems are quite disparate, there is some consistency in operating costs on a dollar per 1,000 gallon

basis. A typical installed cost for a 100 gpm purified water generation is \$1.5 million and with WFI generation by vapor compression the cost rises to \$3 million (between 15,000 and 30,000 \$/gpm). Conversely, a typical 700 gpm makeup UPW plant installed cost is between \$12 million and \$18 million (between 17,000 and 25,000 \$/gpm). Operating costs for a UPW system are generally between 10 and 15 cents per 1,000 gallons, while WFI and WPU water costs vary greatly, between 5 and 14 cents per 1,000 gallons for WPU and between 12 and 21 cents for WFI, depending on the distillation technology. As a basis for comparison, potable drinking water generation typically costs 2 cents per 1,000 gallons.

TREATMENT PROCESSES

Treatment systems are generally designed based on the incoming water quality, the required effluent quality, and the project's reliability, maintenance, and operational criteria. As discussed, there are significant differences in the quality and criteria of water for biopharmaceutical and microelectronics facilities. Both WPU and UPW systems are generally fed from a potable water source. A WFI system is usually fed by a WPU system with a resistivity of between 1 and 5 Mohm-cm and a TOC of roughly 300 ppb. In contrast, the UPW polish system is fed by a primary loop that typically has a resistivity of between 16 and 18 Mohm-cm and a TOC of 30 ppb or less. This results in more treatment operations in a UPW system than in a WFI/WPU system.

Biopharmaceutical Treatment System

Compendial water must be generated from potable water. Drinking water standards are usually set nationally, but in the absence of national standards World Health Organization (WHO) guidelines are generally used. Water purification methods vary widely depending upon water source and municipality. Feed water is pretreated before RO; membranes may become prematurely fouled without adequate pretreatment. As shown in Figure 2, a typical pretreatment and WPU process includes:

- Multimedia filtration.
- Softening.
- Activated carbon adsorption.
- Micron filtration.
- Ultraviolet UV disinfection at 185 nm.
- RO demineralization.
- Continuous electrodeionization (CEDI).
- Submicron filtration (optional).

The WPU source may be utilized to generate WFI by the following methods:

- Distillation (multi-effect or vapor compression); or
- RO unit (only in US and Japan); or
- Ultrafiltration (UF) unit (only in Japan).

Although RO is approved for WFI in the US, it is seldom utilized due to problems maintaining high quality water.

Turbulent flow regimes, elevated temperatures (60 to 85 degrees C) and periodic sanitization (either steam or chemicals) are the main tools available for microbial quality control. Distributing water at elevated temperatures is a generally acceptable microbial control measure. This design has economic consequences: increased rouge potential, insulation and personnel protection, more robust elastomers, and energy costs of temperature maintenance. Many users operate with ambient (cold) storage and distribution loops. Such loops are not viewed as self-sanitizing; in fact they are susceptible to contamination from oligotrophic bacteria; typically *Pseudomonas* types and Gram negative bacteria suited to low levels of nutrients. These organisms are important in the development of biofilm on piping surfaces however they may be planktonic; i.e., within water bulk.

Strict adherence to sanitization schedules and methods is required to control microbial contaminants. Ambient or cold loops are most commonly sanitized by heating to the operating temperatures of hot water systems. New methods of sanitizing without costly heating energy and interruptions to loop operation have been adopted. The introduction and use of ozone has increased in the biopharmaceutical industry. Ozone is a toxic substance in the atmosphere and must be removed prior to water takeoff. Moreover, ozone is a very effective sanitant with cell destruction kinetics orders of magnitude higher than chlorine. Ozone will destroy most bacteria in seconds by lysis of the cell wall.

Microelectronics Treatment System

A typical UPW treatment plant is fed potable water. However, some sites will have their own well-water sources. As shown in Figure 3, the makeup and primary system typically includes:

- Filtration for silt reduction using either multimedia or a membrane ultrafiltration or cross flow microfiltration (as low as 0.05 micron).
- Preheat heat exchanger
- Micron filtration
- Serial (two-pass) RO

- Sterilizing and organic oxidation with 185 nm UV
- Continuous electrodeionization (CEDI)
- Mixed bed ion-exchange resins
- Submicron filtration

The UV/mixed bed deionization/filtration sequence is repeated in a continuously circulating polish loop to ensure reliable supply of 18.2 megaohm-cm water. Depending on the specific specifications, degasifiers (for oxygen removal) are installed upstream of the final mixed beds, 254 nm UVs are used downstream of the final mixed beds and ultrafiltration (6,000 Dalton) is often used as final filters¹¹.

The trend in UPW system generation is towards membrane operations, and away from particulate/resin unit operations requiring periodic regeneration or backwash. This trend is due to cost, reliability, and operational advantages afforded by the former. Sanitization is generally performed chemically, with either ozone or hydrogen peroxide, or peracetic acid, hot sanitization is not typically utilized, except for final ultrafilter sanitization.

MATERIALS OF CONSTRUCTION

To meet facility operational objectives, biopharmaceutical water systems rely heavily on polished and passivated stainless steel as the major construction material, with piping and equipment specified for drainability and compatibility with frequent sanitization thermal cycling. In addition, treatment equipment must be selected that minimize introduction of biological load. The water distribution system is a potential contamination source, each point-of-use valve or instrument take-off represents a possible microbial entry site. These sites and the entire storage and distribution system may periodically require batch re-sanitization.

As metal ions can poison a semiconductor, microelectronics water systems rely heavily on fluoropolymers as the major construction material, and minimize metallics in their polish and distribution systems. Piping systems are designed for reliability, pressure control, and avoidance of extractable contaminants. Water treatment equipment for UPW is selected to eliminate all contaminants, and may create a temporary biological load that will be eliminated in subsequent processing. A circulated UPW distribution system incorporates purification equipment (polish equipment), so the water supply is continuously maintained within specification levels without periodic shutdown.

In spite of major differences in biopharmaceutical and microelectronics objectives and materials of construction, similarities have resulted:

- Valve and component manufacturers for both industries have developed components that eliminate or minimize dead zones and are compatible with various sanitization chemistries and temperatures.

- Piping and component suppliers closely control interior surface finishes to minimize micropores.
- Piping and equipment joining methods have been developed to minimize interior weld beads.
- The same manufacturers supply membranes, filter elements, resins, and other consumables for the common treatment technologies.

Compendial waters for the most part are distributed in sanitary welded 316L stainless steel piping with equivalent grade pumps, heat exchangers, components, and fittings. Silicone, Viton or EPDM elastomers may be used for seals and valve diaphragms. Polyvinylidene fluoride (PVDF) piping is acceptable for exposure to ozone, elevated temperatures, steam and pressure (75 psi at 80 degrees C) and may present a viable piping construction material for certain applications.

Stainless steel water storage and distribution systems for biopharmaceuticals must be properly cleaned prior to initial passivation to reduce corrosion. Passivation is accomplished with citric acid or, more effectively, a mixture of chelating agents. Periodically a stainless steel storage and distribution system will require repassivation to replenish the protective oxide layer. Rouge is low-level iron-oxide contamination, which can adversely affect the piping and product. It can be removed by derouging with agents/acids to reduce ferric iron to ferrous, and organic acids to aid in the dissolution of ferrous ion. Repassivation is required after derouging. Typically a hot WFI system will require derouging every 1 to 2 years and a cold/ambient system every 3 to 4 years.

Striving for minimal metallics and other extractable constituents in the polish and distribution loops, microelectronic UPW distribution lines are almost universally constructed of PVDF, with fluoropolymer coated elastomers and PVDF-line FRP storage tanks. Stagnant regions at valved branches are minimized with molded PVDF zero-static takeoff valves installed at use points. Many facilities will even require their polish mixed beds and final cartridge filter housings be fluoropolymer lined rather than rubber-lined or electropolished stainless steel.

INSTRUMENTATION, CONTROLS, AND ANALYTICAL MONITORING

Both biopharmaceutical and microelectronics high purity water systems generally include PLC-based control systems, with trending capability through a facility management system. Adequate online information is gathered to document critical water quality parameters and to aid in performance trouble-shooting. For both systems, the degree of automation varies with size and cost, but typically is based on continuous operation with moderate operator attention.

CONCLUSION

Because of manufacturing requirements and regulatory conditions, microelectronics and biopharmaceuticals facilities tend to have significantly different capacity and final quality specifications. As a result, the critical treatment technologies vary while pretreatment is similar. Biopharmaceutical high purity water systems tend to be relatively small and more consistent in their design and operation. Through the regulatory process they have integrated treatment technologies and analytical parameters similar to those successfully used in the microelectronics facilities. Microelectronics UPW systems tend to be quite large with minor variations in design and operation. Nevertheless, both capital and operating cost of UPW and WFI, per unit of usage, are quite similar.

Similarities exist in front-end treatment for both industries. Reverse osmosis remains the dominant demineralization process in the generation of high purity waters. Membrane-based CEDI is common place in water intermediate treatment. Beyond this point, the system technologies diverge substantially, utilizing different process equipment and operational concepts.

While biological content of water is a significant factor for both industries, the design and operation of WFI systems is highly directed toward this parameter. Less intrusive sanitization processes are required to diminish the costs associated, both directly and indirectly, with operating at elevated temperatures. Membranes with greater tolerance to contaminants, higher temperature resistances, and increased rejection rates are needed to reduce times between failure and sanitization, before they will gain wide acceptance in the biopharmaceutical industry, especially for WFI generation. Other membrane unit operations will gain popularity in the biopharmaceutical arena as users avoid introduction of added ingredients.

The trends toward water and energy conservation and escalating cost will become factors in the development of more efficient unit operations, an area pioneered by the microelectronics industry. The biopharmaceuticals will be able to leverage these innovations, as allowed by the regulatory environment.

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About the Authors

Andrew Baird Msc Eng. is a process engineer with IDC. The bulk of his work has been in biopharmaceuticals. He obtained a B.S., Biotechnology in 1988 from University of Reading, United Kingdom and a M.Sc., Biochemical Engineering in 1990 from University of Birmingham, United Kingdom. His scope of expertise includes process and equipment design for fermentation and purification of proteins derived by rDNA technologies and utility system design. His experience includes field supervision of an integrated validation team validating a grass-roots biotechnology facility. Andrew can be reached at 60 Pointe Circle, Suite 200, Greenville, South Carolina 29615, (864) 235 3533 (email: andrew.baird@idc-ch2m.com).

Kirsten Sommer, P.E., is a chemical engineer for IDC, and for the past 14 years has been involved in design, construction, and consulting projects for the semiconductor industry. As a chemical engineer, her areas of expertise include ultrapure water systems, recycle/reclaim systems, wastewater treatment systems, and chemical handling/distribution systems. Ms. Sommer has also performed a wide variety of related chemical engineering services for electronics, chemical, printed circuit board, and specialty metals industries. Kirsten can be

reached at 2020 S.W. 4th Avenue, 3rd Floor, Portland, Oregon 97201, (503) 244 6040 (email: kirsten.sommer@idc-ch2m.com).

Ralph Williams, P.E., is a water technologist for IDC, with extensive experience in high purity process systems, water treatment, and in chemical-related code analysis. He has been responsible for management of ultrapure water technology at IDC, and for the last 10 years played a leading role in the advancement of IDC's technological leadership in the areas of ultrapure water, ultrapure water reclaim, waste treatment, and process piping systems. Mr. Williams was previously Vice President of Advanced Industrial Designs, Inc. and Chief Engineer at Balazs Analytical Laboratories. Ralph can be reached at 2020 S.W. 4th Avenue, 3rd Floor, Portland, Oregon 97201, (503) 244 6040 (email: ralph.williams@idc-ch2m.com).