



Design Economics for USP Purified Water Systems

The emergence of reverse osmosis (RO) as a primary deionization technique since the 1980's has all but eliminated the use of regenerable deionization for USP Purified Water production. As RO has become commonplace, innovative or alternate technologies are not often considered. However, RO and RO/ion-exchange (IX) based systems are not always the most economically sensible process for USP Purified Water generation. Inherent to RO system design are stringent feed water requirements, the inability to meet USP on-line conductivity requirements consistently without polishing IX techniques, relatively low system water recoveries, and ongoing maintenance costs associated with cleaning, sanitization and membrane replacement. This paper discusses the current processes used to generate USP Purified Water and proposes a practical approach to determining the best technology choice by investigating the lifecycle economics as well as advantages and benefits of each design scenario.

It is truly amazing that two forward-thinking industries such as pharmaceuticals and biotechnology are so slow to embrace alternate technologies for critical utilities such as pharmaceutical water. While production of Water for Injection (WFI) has been limited almost exclusively to distillation (mostly due to FDA requirements), Purified Water generation has evolved slowly from IX based systems in the 1970's and 1980's to RO based systems in the mid 1980's through today. Ion-exchange, including non-regenerable ion-exchange and electrodeionization (EDI), is mostly limited to RO polishing applications for Purified Water and non-compendial water systems for pharmaceutical manufacturing. IX is also employed frequently as pretreatment to multiple-effect distillation units for WFI generation. While the technology for all these systems continues to improve, non-traditional applications such as the use of distillation for Purified Water generation should be investigated.

Table 1 - Seven Production Methods for USP Purified Water¹

- A. Off-site regenerated ion-exchange
- B. Reverse osmosis/off-site regenerated ion-exchange
- C. Reverse osmosis/electrodeionization
- D. Distillation
- E. Two-pass reverse osmosis
- F. On-site regenerated ion-exchange
- G. Reverse osmosis/on-site regenerated ion-exchange

Purified Water Systems

The ability of current technology to meet USP Purified Water quality requirements is not exceptionally challenging. The maximum allowable conductivity level of 1.3 μ S/cm at 25°C and the 500 ppb limit response for total oxidizable carbon (TOC) are indeed very easily obtained with sound pretreatment and well maintained systems. With the exception of thoroughly removing weakly ionized substances such as ammonium and bicarbonate with RO and distillation units, the ionic and organic challenge for all common processes are relatively feeble based on most feed water conditions. Product water quality failures in Purified Water generation systems typically occur from a lack of microbial control and the inability to meet the USP recommended guideline of 100 cfu/ml, both at the outlet of the generation system and at points-of-use.

The advent of RO based systems as a replacement for IX was primarily driven by favorable economics with higher total dissolved solids (TDS) feed water levels and the elimination of acid and base chemicals required for regeneration of IX systems. Utilization has further increased as the technology of commercially available membranes ad-

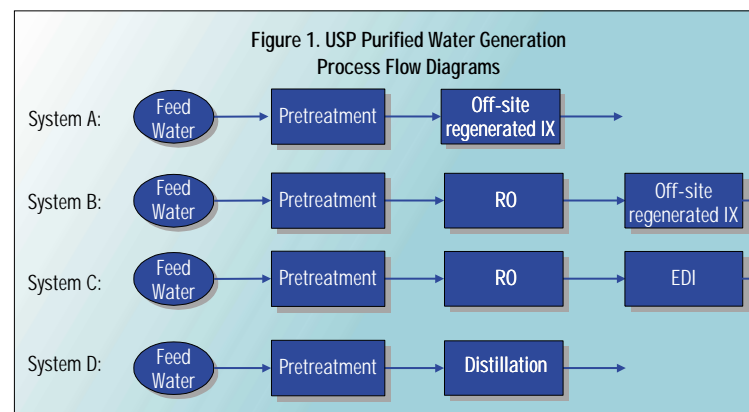
vances (e.g. lower operating pressures, increased rejection, hot water compatibility, etc.). Newly commissioned regenerable IX systems are very scarce in the pharmaceutical industry today in the U.S.

However, the application of IX and related technologies continues to have a role in the biopharmaceutical market. Non-regenerable IX systems, both as a stand-alone system and ionic polishing of RO based systems are popular in laboratory applications, low flow applications, and where capital is limited. These systems involve minimal upfront expenditures, but have higher operating costs associated with external service. EDI is also employed in applications as a polishing technique to RO.

Process Options

The ISPE Baseline Guide for Water and Steam (ISPE Guide) outlines four common processes for USP Purified Water generation; two-pass RO, RO followed by IX polishing, IX, and distillation.¹ The ISPE Guide further delineates these processes into the seven systems listed in Table 1. For this review, we will examine only a fraction of the viable treatment process suggested; eliminating three viable yet seldom used techniques for Purified Water generation. The three possible scenarios mentioned in the ISPE Guide, yet excluded from this review, are two-pass RO, RO followed by on-site regenerated IX and a system inclusive of only on-site regenerated IX. Two-pass RO systems seldom exist for Purified Water generation without a polishing technique and the ability, or inability, for them to produce water meeting USP Stage I conductivity consistently has been discussed elsewhere.² These systems may be considered more frequently when Stage 2 or Stage 3 USP conductivity limits are acceptable. Two-pass RO systems for Purified Water generation are best suited for low TDS feed waters with an absence of significant amounts of choramine or ammonia.³ As mentioned above, the desire to minimize hazardous chemicals in a clean utility environment, has led to a minimal amount of on-site regenerated IX systems installed for Purified Water production. On-site IX systems are typically employed as replacements to existing systems or when the regeneration chemicals are already in place at the site. The storage, handling, and disposal of these chemicals are less desirable for new installations.

Thus, the Purified Water generation processes that will be explored are Systems A, B, C, and D listed in Table 1 and are shown schemati-



cally in Figure 1. The following discussion outlines typical process flow diagrams, with major unit operations shown, for USP Purified Water Generation Systems. Additional equipment may be required for specific operational requirements, feed water qualities, or to obtain final product attributes (e.g. low endotoxin waters).

System A consists of pretreatment followed by off-site regenerated IX. The IX may consist of separate bed (cation and anion) exchange vessels, mixed bed IX vessels, separate bed followed by mixed bed vessels, or other IX configurations. System B includes pretreatment followed by RO for primary ion removal and off-site regenerated IX for

ionic polishing. The RO system may be either single or double pass design. System C is similar to System B with EDI replacing the IX. System D incorporates pretreatment followed by distillation. For this exercise we will consider the use of vapor compression (VC) distillation. This decision is based solely on the frequency of VC for Purified Water vis-à-vis multiple-effect distillation.

There are no methods of production defined by USP for Purified Water, only that it is produced by a suitable process. This results in countless possible design configurations that could be validated to meet the required product attributes. Reverse osmosis has become the preferred method of production due to lower capital costs, an abundance of system and membrane suppliers, and the relative simplicity of operation. RO has the added benefit of removing most impurities found in water both ionic and organic, including bacteria and endotoxin. With proper pretreatment, RO systems reliably produce water for pharmaceutical purposes with minimal preventive maintenance and cleanings required. The minimal amount of chemicals required, either for cleaning, sanitization or upstream pH adjustment also makes RO an attractive technology choice.

When on-site bulk regeneration chemicals are not preferred, IX may be employed in such a system as shown in System A (Figure 2). This system includes pretreatment followed by an off-site re-

generated IX system. Depending on the TDS levels in the feed water, this system may include separate bed, cation and anion, exchange vessels followed by a mixed bed polisher. This three-bed system would easily meet the Stage 1 USP conductivity requirements, often times with product water approaching 0.55 $\mu\text{S}/\text{cm}$ at 25°C. Product water TOC levels will also be well within the maximum USP action level of 500 ppb on most well waters. For high TOC feed waters additional TOC reduction techniques such as activated carbon, ultraviolet (UV) light at 185nm wavelength, or organic scavenging IX may also be supplemented to the system design. While the anion resin also exhibits some adsorbent properties for negatively charged organic molecules, IX resins with low levels of organic leaching may also be used. Of critical importance for these systems is to ensure that the exchange resin is segregated to ensure that the resin is used only in high-purity applications and is regenerated in a cGMP environment. Virgin IX resin is also an option for exchange systems at a higher operating cost.

While the resin replacement can be used as a method of microbial control, hot water sanitization of the systems can be used with less frequently exchanged systems or when the viable bacteria levels in the product water are more stringent than the USP recommended levels. Submicron filters, downstream of the final IX exchange vessel are also routinely used for resin traps and to decrease the frequency of exchanges. UV light at 254nm wavelength may also be used to assist in microbial control of the system. For additional investment, the off-site regenerated IX vessels may be fabricated from all stainless steel components allowing for hot water sanitization of the IX vessels.

System B, shown in Figure 3 is similar to System A except that RO is used prior to the off-site regenerated IX to decrease the ionic loading on the IX bed and the frequency of exchanges. Due to the presence of the RO membranes, additional pretreatment is required. The use of media and cartridge filtration as an RO pretreatment step is particularly required to reduce the Silt Density Index (SDI) prior to the membranes. This reduces the potential for colloidal fouling and allows for more sensible water recoveries across the RO system. Softening of the

feed water is also employed to reduce the potential for fouling of the RO membranes with scaling salts. Both filtration and softening are common RO pretreatment techniques used in the pharmaceutical water industry. Acid addition, to reduce the scaling potential of multi-valent salts is less common, as high pH feed waters are preferred to maximize the removal of bicarbonate alkalinity and thus the quality of the RO product water. Due to the presence of the IX polisher, the product water from System B should approach 0.55 $\mu\text{S}/\text{cm}$ at 25°C quality.

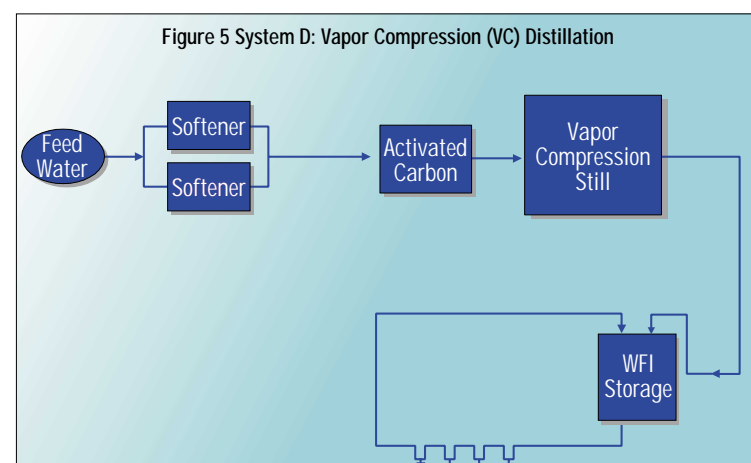
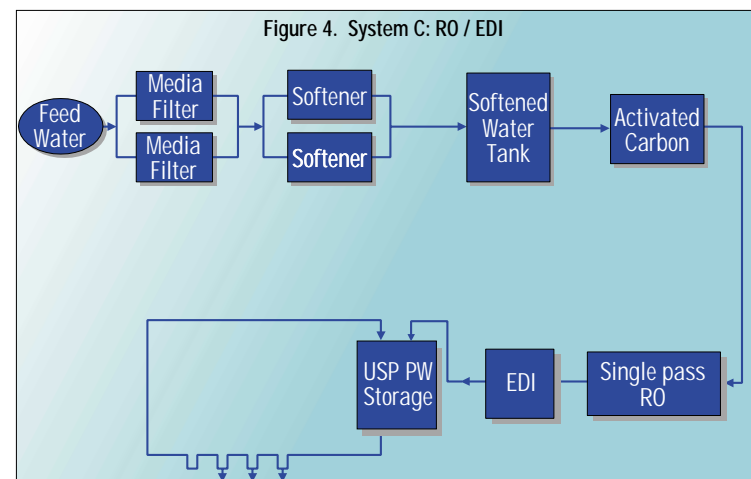
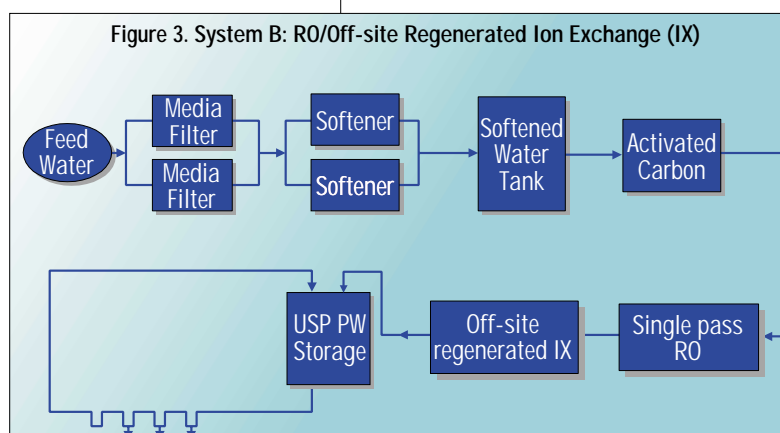
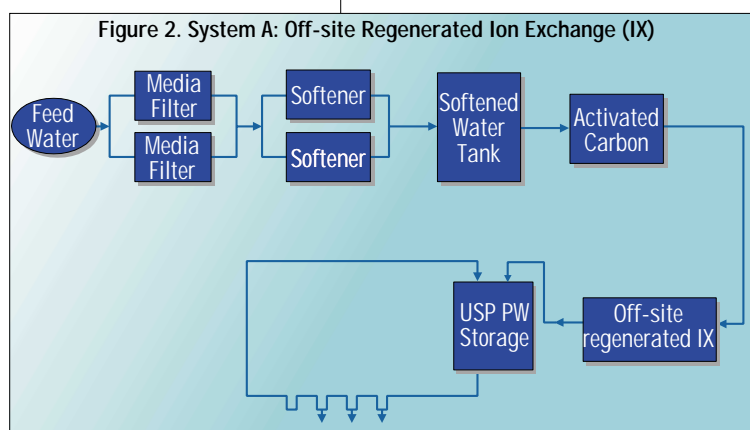
The presence of a softened water tank in System B is added when softened water is required for alternative processes, such as boiler make-up water, or when a portion of the water is recirculated from the RO unit. While not a process necessity, this tank facilitates the system dynamics and allows for RO/DI product water to be recirculated more easily when there is no call for product water from the Purified Water Storage Tank.

Similar to System A, System B does not require bulk chemicals except for those necessary for chemical cleaning and sanitization of the RO system. Both the RO and off-site regenerated IX systems are capable of being hot water sanitized in place with appropriate membranes selection, materials of construction, and pressure and temperature controls. Recently the use of hot water sanitizable generation systems has increased in the pharmaceutical water industry.⁴

Figure 4 shows System C, which uses RO as the primary deionization technique similar to System B, but EDI polishing in lieu of off-site regenerated IX. Therefore, the proposed pretreatment is identical to System C. The use of EDI polishing removes the need for external service and provides water quality that will easily exceed the USP requirements for conductivity. The EDI system may be sanitized chemically or

with hot water (80°C) similar to the RO. The use of chemicals is similar to the RO/off-site regenerated IX system. Final submicron filtration or the use of UV light may be used as an additional polishing technique downstream of the polishing EDI to increase the sanitization intervals. This design is the most common design currently used for the production of USP Purified Water.

System D, shown in Figure 5, shows a vapor compression distillation based system for USP Purified Water generation. The most apparent difference in this system compared to systems A, B and C is the fewer number of unit operations required. This is one of the biggest advantages of VC stills compared to membrane or multiple-effect distillation systems; the pretreatment requirements are less rigorous than other deionization



techniques. Of critical importance for successful operation is the absence of ammonia and chlorine, and the level of hardness and silica in the feed water.⁵ With feed waters of silica content an RO unit may be used upstream of the VC unit to maximize the recovery of the still.

Compared to System A, and the RO-based systems B and C, System D has minimal downtime associated with cleaning and sanitization. System A will require downtime for replacement of the off-site regenerated IX vessels where Systems B and C will require cleaning and sanitization of the carbon and RO, and IX (or EDI) at periodic intervals. The downtime for these systems can be eliminated by the use of redundant trains. While it is difficult to quantify the carbon, RO and IX (or EDI) cleaning and sanitization frequency (due to varying feed water and operational conditions), redundancy is often required when continuous (24/7) water demand is necessary. This can result in significant additional capital investment for these systems. Since periodic sanitization is not required for System D, cleanings are seldom, and only annual preventive maintenance is recommended, it is uncommon to use duplex VC trains; a significant economic advantage for System D.

The process design options shown for Systems A-D use activated carbon for organic reduction and disinfectant removal as a pretreatment step prior to the primary deionization unit operation for consistency in this comparison. Depending on the feed water quality, sodium sulfite injection or UV light may be an acceptable alternate technology choice for disinfectant removal. The use of sodium sulfite includes continuous injection and monitoring of chemical and can simplify operation in certain applications while reducing capital investment. The advantages and disadvantages of residual disinfectant removal techniques has been discussed elsewhere⁶ and is often an end-user driven technology choice.

The non-economic advantages and disadvantages of all of the proposed systems has been summarized in Table 2. System A would require the highest reliance on external service, where System D would inherently require the least amount of service and maintenance due to the fewest number of unit operations required. Again, with proper operation and mechanical design, all of the systems would reliably produce water exceeding the requirements of USP for Purified Water.

Table 2 - Non-Economic Technology Comparison

System	Outside Service Requirement	Ability to vary product water flow rate (i.e. turndown)	Frequency of maintenance (cleanings, consumable replacement, etc.)	Sanitization requirement for Primary Deionization Process
System A— Off-site regenerated IX	Yes	Significant	Less frequent	Less frequent
System B— RO/off-site regenerated IX	Yes (less frequent than System A)	Minimal	More frequent	More Frequent
System C— RO/EDI	None	Minimal	More frequent	More frequent
System D— VC distillation	None	Good	Minimal	Never

Process Design Economics

To correctly evaluate the costs of a pharmaceutical water treatment system, the overall lifecycle cost, including the capital cost as well as the operating cost over the expected lifetime of the system, should be investigated. This simple exercise is a critical process to determine the actual costs that a pharmaceutical water system will incur. A system with a large service component, such as Systems A & B, may be the least expensive to purchase, but require a far greater operating expense. If one can reasonably predict the lifetime of a system, which becomes clearer for production systems rather than those used for research or development activities, one may be able to justify a greater capital investment if a lower operating or overall lifecycle cost is realized. Conversely, if the water requirement is temporary or of unknown duration, a system with minimal capital investment may be an attractive alternative.

For this exercise we will examine the four systems outlined above for

three different flow rates of 10, 25 and 50 gpm. With any piece of capital equipment, the price can significantly vary depending on the features and benefits desired.⁷ The capital cost estimates shown in Table 3 are estimated using current industry averages for USP Purified Water Systems used in a pharmaceutical manufacturing plant. The numbers include the capital cost of the equipment and do not include any installation, commissioning, or qualification costs. The prices include an engineering turnover package to support qualification and a completely-operational factory acceptance test (FAT). Specific features of the systems include an integrated programmable logic control (PLC) system, hot water and chemically compatibility of most major unit operations, and sanitary process contact surfaces downstream of the primary deionization step. All systems are design in accordance with current good manufacturing practices (cGMPs) and in accordance with current industry standards (e.g. ISPE Guide). It is projected that the capital cost of these systems can vary unpredictably based on specific engineering, material, instrumentation (including on-line monitoring), and control package requirements. Additional features and benefits can dramatically affect the cost of all of the systems as mentioned above. As discussed elsewhere,⁸ the price of a particular feature should be compared to the perceived value to conclude whether or not the price can be justified.

Table 3 - Capital Cost Estimates for Various PW System Configurations

System	10 gpm	25 gpm	50 gpm
System A— Off-site regenerated IX	\$52,000	\$64,000	\$76,000
System B— RO/off-site regenerated IX	\$215,000	\$307,000	\$486,000
System C - RO/EDI	\$236,000	\$323,000	\$538,000
System D— VC distillation	\$329,000	\$451,000	\$710,000

Pre-packaged Purified Water System Designs

The costs in Table 3 represent the traditional manufacturing design method of producing individual unit operations, commonly on separate skids or arrangements, and field installing the components to form a functional system. Recently, standardized single-skid construction for USP Purified Water Systems has become popularized in the U.S. As a variation of the traditional, design, specify, and procure for individual packages, individual unit operations may be replaced with completely functional modular water treatment package. The goal is to minimize the overall installed cost and procurement schedule. The capital investment may at times be slightly higher for these modular designs, while installed costs are generally lower. While minimizing space for a modular system, they often contain a greater service requirement than a traditional system; making the lifecycle cost evaluation even more critical.

Operating and Maintenance Cost Development

The development of true operation and maintenance costs is often very challenging. There are direct costs such as utility and water consumption, and others, which are less tangible such as labor and maintenance. Sampling costs are almost never considered when comparing different systems. If one assumes that sampling is required after each unit operation throughout a generation system, then the number of unit operations can have a significant impact on the sampling costs during the Performance Qualification as well as ongoing sampling throughout the life of the system.

Operation and maintenance costs can also be higher for operations such as RO units, which require periodic cleaning. The clean-in-place (CIP) or clean-out-of-place (COP) for the membranes is generally a manual process involving chemicals and labor. RO systems are often required to handle any upset conditions in the pretreatment and be the final reduction mechanism in a Purified Water system for bacteria, endotoxin, and colloidal material, as well as organic and ionic material. With improper pretreatment or varying feed water conditions, RO sys-

tems may be required to be cleaned at intervals as short as 2-4 weeks.

Table 4 shows the assumptions associated with the development of the operation and maintenance costs for the four system designs over the various flow ranges. These parameters will vary from site to site and system to system. National averages have been used as best as possible for the utilities and list pricing for the consumables. Utility pricing can vary dramatically depending on location and availability. Consumable pricing can vary with supplier and volume and frequency of purchase.

Table 5 shows the overall lifecycle costs, including annual operating and capital depreciation over the project lifetime, for the various systems over the range of flow rates. The operating costs developed in Table 5 are shown as an example only, and for one specific case. For one to state that Purified Water is generated at a specific cost lacks significance if none of the supporting economic development assump-

Factor	Cost
Electricity	\$0.07 / KWH
Steam	\$8.25 / Klbs.
Cooling Water	\$0.0035 / KBtu
Feed Water	\$3.75 / Kgal
Waste Disposal	\$0.20 / Kgal
Salt	\$0.07 / lb.
Resin Replacement	\$38.00 / ft ³
Membrane Replacement/ Lifetime	\$2000 / 3 years
Cartridge Filter Replacement / Frequency	\$15 / 3 months
Submicron Filter Replacement/Frequency	\$125 / 6 months
EDI Stack Replacement/ Frequency	\$11,000 / 3 years
Compressor Replacement or Refurbishment / Frequency	\$4,000 (10 gpm) - \$6,000 (25 gpm) - \$8,000 (50 gpm)/ 4 years
Cleaning & Sanitization Chemical Cost	\$4000 / year
Annual Operation	6000 hours
System Lifetime	10 years
Feed Water Quality	300 ppm TDS

tions are listed. For the data presented in Table 5, labor for operation and maintenance is also considered, given it remains a true cost especially for those systems that have a large labor requirement. The data include depreciation of the capital investment listed in Table 3 over the system lifetime; chosen at 10 years for this example.

Some interesting conclusions can be seen from the chart in Table 5. For all systems, annual lifecycle cost is a function of the flow rate. At higher capacities, the cost of water production is always less than lower capacities. This is due to fixed costs of systems, such as sampling, documentation, instrumentation, etc. The lifecycle cost off-site regenerated IX system, however, is a weaker function of the system capacity. The economics of off-site regenerated IX are a direct function of system throughput and feed water quality.

Overall, in this example, the lifecycle economics for the RO/EDI system vis-à-vis the VC system are comparable, even though the RO/EDI system is a lower capital investment for all capacities. Additional capital savings can be realized when there is a requirement for both USP Purified Water and WFI for a single application. By using VC as a method for Purified Water Generation, the product water would easily meet the USP requirements for WFI as well. Thus, production of a single water classification, may allow for additional savings by combining storage and distribution systems. This can result in hundreds of thousands of savings in additional capital investment. Minimization of water classifications throughout facilities is a current trend in the pharmaceutical water industry.⁹

There is a widespread perception that the cost to produce Purified Water ranges from 1-2 cents per gallon. When additional, less predictable costs such as sampling and labor for operation and maintenance are considered, the actual cost of production is slightly higher. For users shackled with capital limitations or unknown (or limited) expected lifetime, higher operating and lifecycle costs may be tolerable.

Table 5 - Annual Lifecycle Cost Estimates for Various PW System Configurations per 1000 Gallons of Water Produced

System	10 gpm	25 gpm	50 gpm
System A— Off-site regenerated IX	\$47.61	\$44.59	\$43.69
System B— RO/off-site regenerated IX	\$45.47	\$39.72	\$36.49
System C— RO/EDI	\$33.32	\$27.74	\$23.23
System D— VC distillation	\$30.40	\$24.12	\$22.35

Conclusions

Distillation has been synonymous with WFI in the pharmaceutical water industry for years. Historically the use of distillation has not been considered for Purified Water generation, except in instances where hot Purified Water has been required. As the capacity requirements for USP Purified Water increase for production waters used in large-scale manufacturing facilities, central utility plants, and CIP waters (especially for biotechnology applications), the use of innovative applications should be explored. The overall lifecycle economics of VC based systems, as well as the capital economics alone, make it well suited for many applications. The emergence of VC for Purified Water applications continues to expand beyond the historical role as a WFI generation technology. The economic viability of this design is enhanced by the downtime often associated with RO based systems.¹⁰

Due to varying feed and product water conditions, site-specific utility costs and availability, and end-user driven preferences, an economic evaluation should be performed for every proposed system. One cannot assume that the process design based on the optimum lifecycle costs will be equivalent for different capacities and applications. This exercise is critical to the basis of design development and can result in hundreds of thousands of dollars in savings over the expected life of a USP Purified Water System. While it is natural to base decisions on capital investment and return on investment while neglecting operational and maintenance costs, a simple economic investigation may reveal unanticipated conclusions.

— by Andrew Collentro

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