WFI GENERATION PERSPECTIVE

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From the USP Pharmacopeia: Reference Water for Injection

"Water for Injection is water purified by distillation or a purification process that is equivalent or superior to distillation in the removal of chemicals and microorganisms. It is prepared from water complying with the U.S. Environmental Protection Agency National Primary Drinking Water Regulations or with the drinking water USP 29 *regulations of the European Union, Japan, or with the World Health Organization's Guidelines for Drinking Water Quality...."*

There are two methods to generate WFI that are accepted by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA), they are distillation and double pass Reverse Osmosis (RO). (Only in the last few years did the EMA begin to accept double pass RO.) In the distillation area, there are two methods of distillation generally utilized in the manufacturing of WFI, Multiple Effect (ME) and Vapor Compression (VC).

In full disclosure, AWS Bio-Pharma Technologies offers all three technologies so my statements are not an effort to push *"the only technology that we have";* but quite the opposite, my comments are based on my experience in the field, primarily from the end user's side, where I spent most of my career.

In my personal experience, VC is the most robust technology with the lowest capital cost and operating cost. Let's review the details:

Reverse Osmosis is technologically a process of dissolved solids reduction (a kind of filtering to use the term loosely). The reverse osmosis (RO) membrane is a spiral wound element that can become fouled by mineral scale, biological matter, colloidal particles and insoluble organic material. Deposits and other material can build up on the membrane surfaces until they cause loss of normalized permeate flow, loss of normalized salt rejection, or both. In addition, the RO process is a delicate balance of flow rates for the supply (feedwater), permeate versus rejectate on both the first and second pass, as well as the volume of water returned for re-cycle through the membranes. Due to changes in the water temperature, fouling of the membranes (and other factors), the system operator must keep a close eye on the performance of the system and adjust the variables on a regular basis. The RO process consumes significant energy due to the high pressure (generally multi-stage) pumps required to provide the hydraulic force necessary for the RO action to occur. The very nature of the process results in membrane fouling, and the membranes are expensive to replace (typically every year or two). The RO systems typically require routine sanitization (either hot water or chemically). Feedwater temperature can have a significant impact on the RO membrane performance, so when feedwater (that may have high seasonal temperature fluctuations) is used, additional steps in the upstream processing must be included to compensate for these (or even more seasonal adjustment and/or changes in performance must be considered).

Next the total consumption of feedwater should be considered. Depending on feedwater quality, atypical double-pass RO system will reject to drain between 15% and 50% (with most systems set up to reject between 20% to 40%) of the in-feedwater; typically, the amount will follow a standard bell curve within these ranges. The rejected water will be high in dissolved solids, but may be suitable for use in boiler feedwater, cooling tower make-up water, or any other purposes where high dissolved solids is not a major concern.

Routine maintenance and diligent daily record keeping is an important part of effectively operating an RO system. Operational data such as total flow (feed and permeate), feed pressure, feed water analysis, inter-stage pressures, chlorine concentration (or other oxidizer), percent recovery and pre-treatment operations, alone or in combination, could have an impact on the RO membrane system performance.

When using a double pass RO to generate WFI, it is generally unadvisable to shut down an RO system at any time (other than during routine maintenance) as when the RO is shut down this is a perfect opportunity for any bioburden on the surface of the membranes to “grow” through the membrane, really defeating the purpose of the system and requiring re-sanitization. Excessive sanitizations, further reduces usable membrane life.

<u>Pretreatment Considerations:</u>
The pretreatment processes upstream of the RO may differ depending upon the feedwater constituents and the user's own preferences or requirements.

<u>The pre-treatment of RO systems</u> requires the removal of chlorine, hardness, and other scales that may form on or damage the membranes. Typically, a general filter (~20 micro) to trap large matter and to protect the downstream components is installed, then duplex water softeners, then either a single or double carbon filter (to remove any chlorine or chloramines), and then a method to remove any ammonia is installed to enhance the overall system performance and longevity of the RO membranes. Note: that while it is possible to get chlorine tolerant RO membranes, they will still be damaged when subjected to long term exposure or excessive amounts of chlorine.

Lastly, the very nature of the RO process is a reduction process with most membranes able to reduce96% <99.5% of the dissolved solids on each pass (depending on the dynamic configuration and performance of the RO system). So on a well-designed and properly operated RO system, consider that the first pass gets 99% of the contaminants and organic matter and the second pass gets 99% of the contaminants and organic matter that remains from the first pass, then the whole system should be able to reduce 99.99% of the contaminants and organic matter (but not 100%). In addition, RO membranes cannot “filter out” entrapped gas, which does negatively impact conductivity measurements of the WFI.

In summary, double pass RO systems are now fully accepted by the FDA (USP Pharmacopeia) and the EMA, but based on the owner’s performance data. However, good science, logic, and experience tells us that double pass RO system are not 100% effective, they require high capital investment and operational costs, and require significant routine monitoring and maintenance.

<u>Distillation</u> has been and is commonly used to produce Water for Injection (WFI) for many decades and is the gold standard from a regulatory compliance standpoint (see above). The two most common forms of distillation (considering water to pharmacopeia standards) are Vapor Compression (VC) and Multiple Effect (ME).

<u>Pretreatment Considerations:</u>
The pretreatment processes upstream of the distillation plants may differ depending upon the feedwater constituents and the user's own preferences or requirements.

- <u>For pre-treatment of ME stills</u> the removal of chlorine, ammonia, hardness, and other scales that may form at the higher operating temperature of a ME distiller is required. Typically, a general filter (~20 micro) to trap large matter to protect the downstream components is installed, then duplex water softeners, then either a single or double carbon filter (to remove any chlorine or chloramines), and then a single pass reverse Osmosis (RO) unit with DI polishing is required. Although not absolutely needed, but frequently deployed, a double-pass RO with DI polishing is also installed (instead of a single pass RO) to enhance the overall system performance and reduce ongoing maintenance of a ME distiller.
- <u>For a VC still,</u> typically the pre-treatment consists of a general filter (~20 micro) to trap large matter to protect the downstream components, then duplex water softeners, then either a single or double carbon

filter (to remove any chlorine or chloramines). Although generally not needed, frequently a single pass reverse Osmosis (RO) unit is also installed to enhance the overall system performance of the VC distiller (this is also typically found where the silica levels in the feedwater exceed the limits of the VC feedwater requirements and to reduce VC system cleaning frequency.

- Here are typical feedwater requirements for ME versus VC stills.

Requirement	ME	VC
Chlorine	0 ppm	0 ppm
Ammonia	0.05 ppm	0.05ppm
TDS	5ppm	500ppm
Hardness	0 ppm	5 ppm
Silica	0.05ppm	< 20 ppm

In summary, the pretreatment requirements for a VC are less stringent than that of ME due to the lower pressure and temperature operating conditions of the VC system.

Technical comparison of the VC distiller relative to that of a ME distiller. VC distillers operate slightly above atmospheric pressure with an associated feedwater vapor temperature of 215°F (102°C) and a compressed vapor (distillate) temperature of 222°F (106°C). The first effect feedwater vapor temperature in a multiple effect unit is typically referred to as the top temperature. Although the top temperature of a ME unit may vary depending upon the design and plant steam pressure, it is normally found to be approximately 350°F (662°C).

Efficiency of Distillation Systems can be defined as Economy (E) and is expressed as the mass of distillate produced per unit of energy input.

- Multiple Effect Systems: Early distillation plants used for water purification boiled raw water within a single "effect" or evaporator at atmospheric pressure with separate condensation to generate freshwater. A typical single effect evaporator operating at atmospheric pressure on a feedwater source at 60°F (16°C) will require 1162 BTU to produce 1 pound (2701 kJ/kg) of water. Utilizing 5 effects in a ME plant reduces the energy input to approximately 425 BTU per pound (988 kJ/kg) of distillate produced. Multiple effect distillation plants use additional effects to improve the economy of the plant by boiling the raw water supply using higher-pressure steam from the preceding effect to generate even more distilled water. Hence, these systems are constructed with multiple effects to sequentially boil feed water under pressure and condense the vapor in succeeding effects. A condenser supplied with cooling water is used to condense the vapor from the last effect and preheat the feedwater to the system. There is a practical limit to the number of effects a ME distiller might have given the rising capital cost associated with each additional effect and the diminishing returns associated with efficiency. But as a general comparison, it would take approximately 9 effects (columns) to provide the same efficiency as a Vapor Compression system.

- Vapor Compression Systems: By contrast, the VC process requires only 130 BTU per lb. (302 kJ/kg) of water produced at 180°F (82°C). If ambient temperature water is produced (as is the case most PW systems), more of the heat within the distillate is recovered and the economy of the VC process improves further such that only 51 BTU are required to produce a pound of water (119 kJ/kg). Therefore, the VC process has very high thermo-efficiency when compared to the ME process.

Vapor Compression Technology:
The major components of the mechanical vapor compression distiller include: evaporator/condenser, a centrifugal compressor, a deaerator (to remove incondensable gases), heat exchangers, pumps, valves, instruments, controls, and associated piping; all consolidated on a single skid.

A typical VC unit used for pharmaceutical distillation requires softened and dechlorinated water (at a minimum) which is boiled inside a bank of tubes. The generated vapor then passes through a mist separator to remove any impurities within the vapor generated from the feedwater supply. The pure vapor enters the compressor, at a controlled saturation pressure (and consequently temperature), where compression takes place, which results in a higher saturation pressure. The higher-pressure (and temperature) compressed steam is discharged into the evaporator onto the outside of the tubes, where it condenses and gives up its latent heat (energy) to the boiling water inside the tubes. The VC process is very efficient thermodynamically, since only about 10-15 BTU (11-16 kJ) of compressor work is used to recycle approximately 1000 BTU (1056 kJ) of the latent heat contained in the released vapors; additional vapor is generated and the process continues. The vapor, which condenses on the outside of the tubes, is collected, and is drawn off by the distillate pump and pumped through a heat exchanger. The excess feed water (blow down) is also pumped through a heat exchanger. Both the distillate and blow down are cooled in their respective heat exchangers, while simultaneously preheating the incoming feedwater. The heat exchangers help to minimize energy consumption of the system. Some make-up heat is required for continuous operation to replace losses within the system, including the terminal temperature difference in the heat exchangers and the heat lost to radiation and venting. This make-up generally provided by either a house (dirty) steam supply or alternatively by electric immersion heaters in our EL series VC units.

Summary of VC Distillation Advantages:
As demonstrated earlier, the feedwater pretreatment requirements for a VC unit are typically less than that of ME distillers. Where feedwater pretreatment can be simplified for the VC installation, the overall capital investment for a VC based system may be lower and the operating costs are lower for the water purification process that employs VC distillation.

Overall VC system capital and operating costs are impacted by:

- ✓ Elimination of cooling water (not required on VC systems),
- ✓ Reduction of the pre-treatment components for VC versus ME distillation,
- ✓ Water recovery rates are typically higher for a VC application (both the VC process and more efficient feed water pretreatment schemes),
- ✓ Lower total energy usage (per unit of WFI generated),

AWS in cooperation with our European partner (Bram-Cor) offers 8 sizes of electrically heated VC distillers that can produce from as low as 66 lph to as much as 1500 lph; in addition, we can also provide steam heated units from 66 lph to 20,000 lph. (see our sales flyer). Of course, we maintain a USA based sales and support team here at AWS to ensure many years of trouble-free service.

Learn more by visiting us at https://www.awsbiopharma.com/pharmaceutical-facilities/water-purification-systems.