# Production of Water for Injection for the Pharmaceutical and Bio-Pharmaceutical Industries

The pharmaceutical and bio-pharmaceutical industries demand high purity water systems that are reliable and capable of consistently providing the required Water for Injection (WFI) and Purified Water (WPU) to meet the established standards of purity. Water for Injection is usually stored in a continuously circulating system & maintained at an elevated temperature to prevent microbial growth. Stainless steel is the preferred material of construction for the tanks, valves, pumps and process piping that make up the high purity water system and the interior surfaces are highly polished and electropolished. The system is necessarily designed to eliminate or minimize "dead zones," thereby avoiding the growth of bacteria. The components of a high purity water system are largely determined by the quality of the water supplied to the plant. Pretreatment is essential and this involves filtration, the removal of chlorine compounds present in the water and percolation through ion exchange media. In addition, to obtain the required quality of WFI, distillation or reverse osmosis filtration must be used for the final step.

Thirty years of working with the processing industries has allowed A&B Process Systems (Stratford, Wisconsin) to gain valuable experience in the design, fabrication and installation of high purity water systems and the several unit operations involved, i.e., filtration, ion exchange processes, reverse osmosis and distillation. Furthermore, the benchmarks of this service are consistent, high quality workmanship that provides a reliable product, as well as the ability to meet design and fabrication challenges. A&B Process Systems is renowned for providing quality of workmanship that is evident in all phases of the project --- the design, the fabrication, the incorporation of automation and computerized controls, the attention to the surface finish of the piping, equipment and all weld areas and finally the installation.

It is critically important to the pharmaceutical and bio-pharmaceutical industries that a high purity water system is reliable and able to consistently produce water that is "in compliance." This means that both the Water for Injection and Purified Water meet the specifications given in the United States Pharmacopeia ( the official document listing all drugs and medical products, together with standards established for the manufacture, dispensation and use of those products)The ability of the product from the high purity water system to remain consistently " in compliance" depends largely upon the design, the operating conditions and the materials of construction used.

## What are the usual operating conditions to produce WFI?

Water for injection is typically stored in a continuously circulating system maintained at an elevated temperature (a temperature of 80-85˚ C is recommended). The circulation of the purified water, under conditions that provide turbulent flow, maintains the elevated temperature uniformly throughout the system. These operating conditions prevent microbial growth and ensure that the water meets the specifications given in the US Pharmacopeia. Although lower temperatures may be acceptable, it becomes necessary to provide sufficient data to validate this mode of operation.

### What factors are of importance to the design of a high purity water system?

It is recognized that the high purity water system is a potential source of contamination, since each point-of-use valve and instrument take-off represents a possible microbial entry site. It is therefore necessary that the piping and equipment be designed to allow the system to be drained easily and frequently sanitized. It is also important to eliminate or minimize "dead zones" in the system, again to avoid the growth of bacteria. A&B Process Systems have extensive experience in the design of these systems, a result of three decades of service to the processing industries.

### What material of construction is recommended?

The preferred material of construction is polished and passivated stainless steel. The interior surfaces of the piping, valves and pumps should be highly polished, to minimize the number of micropores in the metal surfaces, these being sites for both corrosion and microbial growth. The techniques used to join piping and components can also be of concern and experience has taught the industry that it is important to minimize the number of weld beads in the system. A&B Process Systems are nationally recognized for their ability to fabricate stainless steel process equipment and process systems.

### What components are required for a high purity water system?

The components of the system are largely determined by the quality of the water supply to the plant. Pretreatment of the feed water is essential, even when the water supply meets the standards for drinking water. The pretreatment typically requires multiple unit operations, including filtration through membranes of various pore sizes, the removal of chlorine and chloramines using activated carbon beds and percolation through ion exchange resins to remove soluble ionic species. This pretreatment sequence effectively reduces the conductivity of the water, as well as the levels of organic contaminants, suspended solids and colloidal particles present. However, to produce the required quality of water for injection it is necessary to include either distillation or reverse osmosis filtration as a final step.

### What is distillation?

Distillation is simply the phase change from liquid to vapor, thus enabling the pre-treated feed water to be stripped of any residual ionic materials, particulates, colloids and non-volatile organic compounds. Distillation also removes bacterial endotoxins. This is crucial to the production of the water for injection. The evaporation stage of the distillation process leaves the non-volatile compounds and large particulates in the feed water. The presence of demisters and separation devices removes any of these materials that may be entrained in the vapor.

There are several types of distillation units in use in the processing industries, e.g., single effect, multiple effect and vapor compression units. A single effect unit consists of a series of columns within which the phase change occurs, the evaporation and subsequent condensation being considered as a single effect. The feed water may be heated externally before entering the main evaporation column or the main column itself is heated. Single effect distillation units are

suitable for production of purified water at rates up to approximately 120 liters per hour. For larger outputs it is necessary to use multiple effect units, in which the steam generated in the first effect is used to heat the feed water in the second effect and so on. With both types of distillation unit the distillate is typically gravity fed to the storage tank, requiring that the outlet from the unit be higher than the inlet to the tank and, if possible, within close proximity. In this way the need for transfer pumps or extensive piping in the system can be avoided. In contrast, a vapor compression unit initially generates steam at a low pressure in an evaporation vessel. This steam is then compressed, allowing it to be heated to higher temperatures, before being returned to heat incoming feed water and simultaneously be condensed to the high purity product. The vapor compression unit relies upon the use of pumps and compressors, which results in more service and maintenance requirements than a multiple effect distillation unit, although its' demand on plant utilities is lower.

### What is involved in reverse osmosis filtration?

Reverse osmosis is a process in which water is forced through a semi-permeable membrane and the pores in that membrane effectively reject dissolved ions, salts and organic compounds. The process may be regarded as filtration on a " molecular and ionic level." The performance of the process is dependent upon several factors, e.g., the quality of the feed water, the size of the unit, the type of membrane, the operating pressure and temperature. The membranes are fabricated from cellulose acetate, cellulose triacetate, aromatic polyamide resins and mixtures of these materials. The use of the non-cellulosic membranes can be advantageous, since these membranes can be operated at lower temperatures and over a wider range of pH than their cellulosic counterparts. Furthermore, the non-cellulosic membranes are not susceptible to oxidative degradation by any bacteria in the water, eliminating the need for a disinfectant in the water undergoing the reverse osmosis process. A reverse osmosis system typically contains several components, including the filtration units that are located before and after the modules containing the membranes, a booster pump to increase the net pressure across the membranes, storage tank(s) and a control panel. (Note: In the case of a system to produce water for injection, the pre-treatment filtration unit will already be included.) Reverse osmosis units can be designed for industrial applications requiring production capacities ranging from 600 to 50,000 gallons per day of high purity water.

### What other factors are important when installing a high purity water system?

It is essential that the new high purity water system satisfy the validation process. It is also required that any changes or additions to an existing water system also satisfy the validation process.

### What is this validation process?

There are three formal stages to the validation process, these being installation qualification, operational qualification and performance qualification. Installation qualification establishes that the system conforms to the design drawings, specifications and manufacturer's

recommendations. The second stage demonstrates that the operation of the system and the equipment is as was specified. The validation process is completed after it has been shown that the performance of the system meets all the process requirements under simulated production conditions. Design changes to an existing high purity water system must again satisfy this validation process. Thus it is a challenge to design, fabricate and install a system to produce water for injection for these industries. For an organization faced with this challenge, it is beneficial to work with a company with demonstrated capability and extensive experience in the processing industries.

## Is A&B Process Systems such a company?

A&B Process Systems is nationally recognized for the design, fabrication and installation of stainless steel tanks, vessels, auxiliary equipment and piping, including the high purity and hygienic piping required by the pharmaceutical and bio-pharmaceutical industries. The company's reputation has been built upon the capability to produce high quality products to meet performance requirements in a timely manner. A&B's success is attributed to their in-house resources, i.e., the design and fabrication engineers, the welder-fabricators and welder-fitters, the automation and controls group and its' QA/QC professionals. The company has four plants in Stratford, Wisconsin, with approximately 80,000 square feet of manufacturing capability. Plasma cutting, automated seam welding, GMAW, GTAW and orbital welding capabilities are available when needed. An extensive range of process equipment may be fabricated in these facilities to meet customer requirements. The company also offers an experienced management team, capable of coordinating all aspects of a particular project, e.g., site preparation, selection and scheduling of general contractors, cost estimation, delivery and installation of the new equipment.