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API Pharmaceutical Water Systems Part I: Water System Design

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Introduction

The design of a pharmaceutical water system for the active pharmaceutical ingredient (API) industry will depend on the type of API process (e.g., intermediate API, final API, API cleaning):

- Final API: This is the final product-manufacturing step in the process and is the substance in a pharmaceutical drug that is biologically active.
- Intermediate API: Most chemical reactions require more than one step to complete. An intermediate is the reaction product of each of these steps, except for the last one that forms the final API (i.e., final product).
- API cleaning: This is the term used to denote if the water will be used for equipment cleaning after a final or intermediate API.

This paper will cover the following:

- Determining the required water quality grade for an API process
- Typical municipal and purified water designs
- General purified water design considerations.

Determining the Required Water Quality Grade for an API Process

Below is a typical table that could be used when determining the required water quality grade for an API process.

Type of Process/Product	Type of Water System Required
Initial and Intermediate API Steps	Water equivalent to the local drinking water requirements (i.e., municipal water). Normally water is used as municipal water.
API Cleaning (except final API rinse steps)	Water equivalent to the local drinking water requirements (i.e., process water)
API Final	USP/EP purified water
API Cleaning (final rinse steps)	USP/EP purified water

Note: USP: United States Pharmacopeia (i.e., US Food and Drug Administration regulatory requirements)
EP: European Pharmacopeia (i.e.,European regulatory requirements)

The justification for a lower water grade quality to be used in the API initial and intermediate steps is as follows:

- There is typically further solvent addition and/or distillation prior to commencing the manufacture of the final API.
- Solvent additions and/or a distillation minimize the growth of microorganisms.
- The risk impact to the final API is minimized by the subsequent solvent addition and/or distillation prior to commencing the manufacture of this step.

In the event where there is no further subsequent solvent addition or distillation preceding the water addition (i.e., typically API final isolation), a higher water grade is required to minimize the impact to the final API.

Typical Municipal and Purified Water System Design

Municipal Water System Design

Municipal water (i.e., water equivalent to the local Environmental Protection Agency [EPA] drinking water guidelines) or deionised water is typically the input to the purified water system. The municipal water generation system typically incorporates a storage tank, chlorine dosing unit, and the distribution network. A set of sand filters is used for preliminary filtration. In some cases, ultrafiltration (UF) units are also present before the chlorine-dosing unit.

Sand filters work by providing the particulate solids in the water with many opportunities to be captured on the surface of a sand grain. They are usually used to separate small amounts of fine solids from aqueous solutions and are usually used to purify the fluid rather than capture the solids as a valuable material. Therefore, they are mostly used in water treatment.

UF occurs when a pressure forces a liquid against a semi-permeable membrane. Suspended solids of high molecular weight are retained while water and low molecular solutes pass through the membrane. The membrane chosen must be able to withstand the type of microbiological organism present in the water system and the incoming water type (i.e., the ability to reduce the water color and total viable count to the municipal water specifications):

- Total viable count is a measure of the quantity of microorganisms such as bacteria, yeast, and mold in the water system.
- A synthetic type membrane rather than a cellulose type membrane should be used for a water type application. In the event of any water stagnation, a synthetic type membrane will minimize the formation of microbes. A cellulose type membrane can be metabolized by bacteria thus leading to the degradation of the membrane surface that in turn leads to a loss of retention in the membrane. The synthetic type membrane is indigestible by bacteria, has a higher tensile strength, and is more rigid therefore less resistant to handling damage.

Purified Water System Design

The purified water generation system takes the feed water input (i.e., municipal water or equivalent), dechlorinates to reduce chlorine levels, and softens to remove water hardness. To meet purified water microbiological requirements, reverse osmosis (RO) is the preferred technology; however, other technologies may also be used. To meet purified water conductivity requirements electrodeionization (EDI) is the preferred technology; however, mixed-bed deionization may also be used. The resultant water is then passed through an ultraviolet lamp and then stored in the main purified water storage tank. The purified water distribution loop takes water from the storage tank and back to the storage tank in a continuous loop. Use points are included on the distribution loop so that water can be delivered to the plant when required. Below is a typical purified water system design.

Additional Technologies

- In the normal osmosis process, the solvent naturally moves from an area of low solid concentration through a membrane to an area of high solid concentration. Reverse osmosis is applying an external pressure to reverse the natural flow. RO is most commonly known for its use in drinking water purification from seawater (i.e., removing the salt and other substances from the water molecules).
- EDI utilizes an electrode to ionize water molecules and separate dissolved ions from water. It is done without the use of chemical treatments and is usually a tertiary treatment to RO.
- UV sanitization uses a UV light source (lamp) that is enclosed in a protective transparent sleeve (usually quartz). The lamp is mounted such that water passing through a flow chamber is exposed to the UV-C light rays. When microbes

are exposed to the UV rays, they are rendered sterile and can no longer reproduce. The microbes are now considered dead:

- UV water treatment does not introduce any chemicals to the water, it produces no byproducts, and it does not alter the taste, pH, or other properties of the water.
- The use of UV lights is not recommended as the primary means for controlling microbial growth. UV lights can be used in conjunction with other (such as 0.2 micron filters) pretreatments units to provide secondary microbial control. Typically UV lamps are installed after the EDI unit. UV intensity should be monitored and documented.

General Purified Water Design Requirements

Design Element	Requirement
Pretreatment Unit Operations	• Filtration, softening and de-chlorination.
Pipework Specifications	• The fabrication should address weld quality requirements, welder's qualification, welding procedures, w processes, and passivation requirements and documentation.
Pipework Material of Construction	• Prior to dechlorination may be copper, Poly Vinyl Chloride (PVC), or other suitable polymers. • Purified water storage and distribution pipe work must be of sanitary design. • If stainless steel is nominated as the pipework material of construction, the grade must be 316L and a finish equal to or better than 0.5 µm Ra.
Dechlorination System	• Must be designed to prevent microbial contamination and also ensure the levels are low enough prior the RO unit. • RO units typically cannot tolerate more than 1.5 ppm of chlorine. • Increased chlorine levels can affect membrane operation.
Antiscale	• Antiscale is used to reduce the calcium carbonate content entering the RO unit. • Increased levels can lead to RO membrane blockages.
Water Conductivity Leaving the EDI	• It is necessary to ensure that the water conductivity is not too low. • An increased level of power is required for the unit to operate. • Long-term increased levels of power will lead to operational problems with the EDI unit
Distribution Loop Flow	• Must be designed for a minimum velocity to maintain turbulent flow. • The Reynolds number (i.e., diameter of pipe work x velocity x density/viscosity) can be used to determ whether a certain velocity is sufficient to maintain turbulent flow in the distribution loop pipe work. • Turbulent flow is present when the Reynolds number is greater than 4000. • These flow conditions should be determined when no sample valve is in operation. • Dead legs should be minimized. See section on dead legs below for further details.
Return Flow	• The distribution system should be designed to ensure a return flow. • A back-pressure control valve should be installed to ensure constant return flows to the storage tank in where several sample valves use points are in operation.
Dead Legs	• Distribution system should be designed to minimize dead legs within the system. • No dead legs should exceed an L/D ratio of 6 where L = pipe length and D = pipe diameter. • The goal is to achieve zero dead leg on the system.

Distribution Loop must be Fully Drainable and be of Sanitary Design.	• The slope of distribution system process pipe or tubing should be a minimum of 5.2 mm/m or approxin slope. A slope of 10.4 mm/m or approximately 1% is recommended.
Storage Tank	• Turnover is typically once/hour. This varies depending on system use. • Must be designed with a vent filter and should allow for integrity testing.
Filters on Distribution Loops	• Usually not present on water systems distribution loops as it creates a surface for microbial growth. In- may only be used when particle removal is of concern at any unit operation.
Pumps	• Should be centrifugal and of sanitary design. Pumps must be connected using sanitary clamp connect ease of service. • Backup pumps are typically not allowed as it creates a surface for microbial growth. They can be used cycling regularly between pumps and sanitising. Therefore, it is better not to use them.
Temperature	• Should be kept outside the range of 25 to 65°C. Microbial growth is minimized above and below this te range.

Sanitization	• It may be necessary in piping systems where there are water pipes with drop loops or dead legs. Sani should disinfect the water piping system, providing these benefits:
	  ○ Removal of any biological growth or contamination.
	  ○ FDA compliance.
	• For hot water sanitization, the internal components should be constructed of stainless steel. No PVC i components are allowed.
	• Heat exchangers are used on the distribution loop to maintain the temperature at approximately 20 to to heat the loop to 85°C when required for water sanitizations.
	• Sanitization typically takes place when using water at 85°C. The heat exchangers should be designed drainable and of sanitary design. EPDM seals are recommended for the heat exchangers. There shou differential pressure with the higher pressure on the product side.
	• Chemical sanitization can also be used.

Local EPA Drinking Water Guidelines	• Data is required to verify that the purified water feed input meets the local drinking water regulation re as per USP. • The purified water feed input quality data should address any seasonal variation associated with the g location. For example, the Irish EPA drinking water bromine specification is relatively low. In the event purified water feed input has been manufactured on-site, it may be necessary to source chlorine with l content (e.g., if chlorine is used in the process water generation system) in order to meet the EPA drin bromine specification.

Valves
(i.e., sample valves and valves used for operation)
	• Should be a diaphragm valve sanitary design (Ethylene Propylene Diene Monomer (EPDM diaphragm Polytetrafluoroethylene seal (PTFE) to maintain the integrity of the distribution system:
	  ◦ EPDM exhibits satisfactory compatibility with hot and cold water and has a high heat resistanc
	  ◦ PTFE is very non-reactive partly because of the strength of the carbon and fluorine bond. PTF as it is non-reactive and water will not adhere to surfaces.
	  ◦ The combination of EPDM and PTFE are used due to the following reasons:
	    ▪ EPDM is used in the diaphragm as it is an elastomer and has the ability to deal with the and closing the valve. Therefore, any cracks would not be formed, and a surface for mi growth would not be created.
	    ▪ PTFE is a rigid structure and, therefore, would create a good seal when the valve is clo Hence, this would prevent the stagnation of water around the valve locations, and a su microbial growth would not be created.
	  ◦ Where possible, the location of the valve must be readily accessible and located vertically. No be attached to water points when not in use. This creates a surface for microbial growth and w sample failures.

Notes:

- Passivation is a cleaning process used to remove iron and other contaminants from the surfaces of corrosion resistant steel parts to ensure that a uniform formation of a passive layer is obtained.
- Passivation is most typically a treatment with a citric acid solution that will remove the surface contamination but will not significantly affect the stainless steel itself.

Conclusions

- Municipal water is a non-sanitary type water system; hence, it is required to comply with the local drinking water regulations.
- Purified water is a sanitary type water system and must comply with USP and EP requirements.
- The required water quality grade for an API process is determined by where it is used in the process and the impact of water out-of-specification (OOS) on the final API product.