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Navigating High Purity Waters

"Water, water everywhere, nor any drop to drink."
- Rime of the Ancient Mariner

As the sailor narrating the "Rime of the Ancient Mariner" knew all too well, all water is not the same. The scarce water rationed by the crew was life-sustaining while the abundant seawater below their ship could kill them if consumed.

Today's scientist may not face such dire consequences as the Ancient Mariner, but selecting the correct grade of water is critical for performance, cost management and safety. For many manufacturing and laboratory applications, regulatory compliance is also a key component of the selection process.

This white paper is intended to assist scientists with navigating the selection process through the many different grades of high purity water and their various applications.

Once the grade of water is determined, the question is, can the required water be produced in-house or will it need to be outsourced? Organizations determine this by comparing equipment cost, validation, maintenance, ongoing QC testing, and documentation, with the cost of outsourcing the volume of water required.

While in some cases it may be feasible to produce high purity water on-site, often outsourcing the water supply is the best option. Outsourcing from commercial producers can provide various benefits, including factors such as consistency, documentation and traceability that are typically required for the intended process.

There are dozens of high purity water products on the market today. Outsourcing water may be a very good option for a number of the scientific applications encountered in FDA-monitored facilities.

Water covers more than 70% of the surface of the earth, and is abundant in manufacturing processes for reagents, pharmaceuticals, semiconductors and other products. Many of the applications encountered in these manufacturing processes are unique, having their own set of quality requirements. Understanding the nuances between the many grades of purified water can be daunting, and choosing the wrong type can have significant consequences to businesses. This white paper describes the wide range of high purity water available to manufacturers, simplifying the steps for selecting the correct grade for each application.

All "Pure" Water is Not the Same

It is reasonable to assume that all "pure" water is the same and is appropriate for almost any application. However, this is not the case. As we dive deeper we find a range of specifications that strictly define many different grades of pure water. While a single grade of pure water may fit a range of applications, only rigorous testing can verify the absence of specific contaminants. Such testing and documentation utilizes internal resources and can be cost-prohibitive to perform in-house.

Control of contaminants is a primary objective for any water used in FDA-monitored processes as contaminants can cause safety or product performance concerns. The final product will dictate what level of purity is required. Microbial growth, bacterial endotoxins, disinfection by-products, metals, particulates or chemicals that leach from packaging materials are all monitored at some level for most applications.

In order to provide purity standards for the many purposes water serves in food and drug manufacturing, a range of water purity grades have been defined by the U.S. Pharmacopeia (USP), the European Pharmacopeia (EP) and other scientific organizations.

Water is generally characterized by USP as either water for which there are USP monographs (detailed dissertations for specific production, processing, distribution or usage) or water for which there are no published monographs.

USP monographs for water fall into two categories, either bulk water, which is produced onsite where it will be immediately used; or packaged water, which is produced, packaged and sterilized to prohibit microbial growth. Other bulk waters exist for which there are no USP monographs. These are described in the following sections.

Bulk Monographed Water

Bulk monographed waters are produced onsite, typically in large volumes using multiple in-line purification methods, and then piped to the nearby location for use. USP monographs exist for purified water, water for injection, water for hemodialysis, and pure steam.

Purified Water

Purified water is an excipient used in production of non-parenteral applications, including cleaning of certain equipment. Preparations of purified water must start from water with a minimum purity equivalent to drinking water that is further purified using deionization, distillation, ion exchange, reverse osmosis, filtration or other suitable purification procedures (each procedure must be validated). The purified water may also be bulk packaged to sterile purified water standards. Since packaged purified water may not be used immediately, care must be taken to store the water to reduce microbial growth (e.g., use soon or refrigerate) and to use containers composed of non-leaching materials.

Water for Injection

While care may be taken to eliminate microbial growth, potential residual bacterial endotoxins should also be of concern to the manufacturer. Endotoxins consumed orally are of less concern since they are generally tolerated in the alimentary canal. Parenteral drugs (non-oral drugs such as via injection) present a special concern for endotoxins, as bypassing the alimentary canal may cause an immune response in the bloodstream. Water for injection (WFI) must start from water with a minimum purity equivalent to drinking water that is further treated to meet purified water standards, plus additional bacterial endotoxin specification (and stored/distributed with minimization steps for incoming endotoxin). WFI may also be bulk packaged if tested for bacterial endotoxins and packaged to sterile purified water standards with non-leaching materials.

Water for Hemodialysis

Water for hemodialysis is generally used to dilute hemodialysis concentrates. This water is produced onsite from EPA drinking water further purified to reduce chemical and microbiological components. Water for hemodialysis may also be packaged and stored in non-leaching containers that prohibit bacterial growth. This water product also includes specifications for water conductivity, total organic carbon, microbial limits and bacterial endotoxins.

Pure Steam

Although distillation of water by evaporation followed by condensation is a means of purifying water, care must be taken to ensure that the source water will not contain undesirable residues when converted to steam. Pure steam must be prepared from pretreated source water or similar to purified water or WFI, then distributed under pressure. Pure steam applications include porous material sterilization, product or cleaning solutions heated by direct steam injection, or humidification of processes where steam injection is used to control the humidity inside processing vessels.

Packaged Monographed Waters

Packaged monographed waters may be used in lieu of bulk water they were derived from such as purified water or water for injection. These waters may have specific intended uses as indicated by their names and may also have restrictions on packaging configurations related to those uses. Based on various clinical applications, various packaging configurations such as glass, plastic, plastic bags, or syringes are used to store the different sterile water products.

USP Sterile Purified Water

Purified water that is packaged and rendered sterile is typically used in the preparation of non-parenteral compendial dosage forms or in analytical applications requiring purified water.

USP Sterile Water for Injection
Water for injection is packaged, rendered sterile, suitable for prescription compounding and may be used as a sterile diluent for parenteral products. It is hypotonic, nonpyrogenic, and contains no bacteriostatic or antimicrobial agents.

USP Bacteriostatic Water for Injection
Water for injection that is packaged in single-dose or multiple-dose containers and to which has been added a suitable antimicrobial preservative. It is intended to be used as a diluent in the preparation of parenteral products typically for multi-dose products that require repeated withdrawals.

USP Sterile Water for Irrigation
Sterile water for irrigation, USP may be classified as sterile non-pyrogenic water intended for sterile irrigation, washing, rinsing and dilution applications. It is intended for use only as single-dose or short procedure irrigation and is usually packaged and is sterilized in single-dose containers of 1 liter. This makes it suitable for rapid delivery of a relatively large volume of water.

USP Sterile Water for Inhalation
Water for injection is packaged, rendered sterile and intended for use in inhalators and inhalation solutions. It carries a less stringent specification for endotoxins than sterile water for injection and is therefore not suitable for parenteral applications.

Non-monographed Manufacturing Waters
Other non-monographed waters may be used in pharmaceutical processing such as cleaning, synthetic steps or as starting material for further purification. The water grades meeting these criteria are drinking water and hot purified water.

Drinking Water
Drinking water is defined as potable water that complies with standards of NPDWR, EU, JP or WHO drinking water guidelines. This is the minimum quality of water that should be used for the preparation of bulk pharmaceutical ingredients. Drinking water is the prescribed source for feed water for the production of bulk monographed pharmaceutical waters.

Hot Purified Water
Hot purified water is defined as purified water that has been heated to an application specific temperature to improve solubilization of other ingredients.

Non-monographed Analytical Waters
Non-monographed water may also be used in a wide range of analytical applications. There are almost 20 types of non-monographed analytical waters listed in the pharmacopeia reference. Any analytical water must be evaluated on an application-by-application basis by the user to ensure its suitability for the application.

Non-monographed Analytical Waters		
Distilled water	High purity water	Oxygen-free water
Freshly distilled water	Deaerated water	LAL reagent water
Deionized water	Recently boiled water	Organic-free water
Freshly deionized water	Ammonia-free water	Lead-free water
Deionized distilled water	Carbon dioxide-free water	Chloride-free water
Filtered or particle-free water	Ammonia-free and carbon dioxide-free water	Hot water

Common Laboratory Applications
For analytical applications and assorted other test methods, water specifications have been defined by USP and by the American Society for Testing and Materials (ASTM) for use in their assays.

These grades are not specifically mentioned in the pharmacopeia reference as analytical waters. Many of these grades are application specific and as a group they represent many of the routine procedures currently being performed in labs. As an added bonus for today's busy scientist, these are all commercially available.

HPLC Grade, LC/MS Grade
There are many considerations when using water intended for chromatography applications (HPLC, GC, IC) as it must be free of contaminants. Organic compounds, high ion concentrations, particles, or bacteria can all affect the separation process and/or result in ghost peaks. Applications for HPLC water and trace metal analysis require water conforming to highest purity specified under Type 1 by ASTM. Such water requires mixed bed deionization and filtration with 0.2 µm membrane filters.

Reagent Grade Water / ASTM Type Water

Reagent grade water is defined as water suitable for use in a specified procedure such that it does not interfere with the specificity, accuracy and the precision of the procedure.

ASTM has set standards for four unique purity levels of Reagent grade water. ASTM methods define many chemical analysis and physical testing procedures. These applications will make use of Type I, II, III, or IV water. Each procedure will typically designate what level of water purity is required. Each type designates a specific level of purity for contaminants.

Water Specifications for ASTM Methods

	Type I	Type II	Type III	Type IV
Electrical conductivity, max, µS/cm at 298 K (25°C)	0.056	1	0.25	5
Electrical resistivity, min, Mcm at 298 K (25°C)	18	1	4	0.2
pH at 298 K (25°C)	*	*	*	5.0 to 8.0
Total organic carbon (TOC), max, µg/L	50	50	200	no limit
Sodium, max, µg/L	1	5	10	50
Chlorides, max, µg/L	1	5	10	50
Total silica, max, µg/L	3	3	500	no limit

**The measurement of pH in Type I, II, and III reagent waters has been eliminated from this specification because these grades of water do not contain constituents in sufficient quantity to significantly alter the pH.*

Molecular Biology Grade Water

Biological research labs, DNA labs, and forensic labs utilize molecular biology grade water. These are tested to detect the presence of DNase, RNase, protease, or endotoxins. If any of these are present in the water, it could negatively affect results of many molecular biology procedures.

Cell Culture Grade Water

While there is no official compendium for cell culture grade water, it is loosely defined as, "has proven to be effective in growing cells." Frankly, any USP WFI quality water is adequate for this application. It comes with the most critical characteristics as it is sterile and it is low in endotoxins.

In-Lab Systems

Most of these analytical grades can be produced on-site. Water purification systems, like the ones shown here, can be wall mounted or set up on the benchtop.

These units are available in a wide range of configurations geared toward specific applications. Many of these units can produce up to 200 liters per day.

Endotoxin Considerations

Bacterial endotoxins have been mentioned in several sections above. It is a common theme because the effects of endotoxins can lead to numerous adverse biologic effects in humans and animals. Conditions such as fever, infection and even an altered resistance to infection can be attributed to endotoxins. In rare cases, endotoxins can also produce severe diarrhea and hemorrhagic shock.

If your company is producing an injectable product, the level of endotoxins is an important consideration when selecting a specific grade of high purity water for your process. For injectables, you are likely looking at a sterile version of USP or USP/EP WFI quality water. These compendial waters have an endotoxin specification of 0.25 EU/ml. Water products of most commercial suppliers have actual endotoxin levels that are much lower than that.

One should be leery of endotoxin-free claims as this can be misleading. The lower limit for endotoxin detection is 0.001 EU/ml so no commercially-available test method can accurately measure below that level. While the product may prove to be very low in endotoxin levels it is not possible to fully guarantee the product is completely endotoxin-free. Spectrum Chemical's bioCERTIFIED™ products are tested for endotoxin and other parameters before being released for sale.

What are endotoxins?

Endotoxins are lipopolysaccharides found in and shed from outer membranes of certain gram-negative bacteria. Endotoxins are not secreted but are released only when the cells are disrupted.

Endotoxins may occur as clusters of lipopolysaccharide molecules associated with living microorganisms, as free floating fragments of dead microorganisms, or as the polysaccharide slime surrounding biofilm bacteria. Gram-negative bacteria that form biofilms can become a source of endotoxins in pharmaceutical waters.

What are biofilms?
A biofilm is described as a group of microorganisms in which the cells stick to each other. Often, these cells adhere to a surface.

These adherent cells are frequently embedded within a self-produced matrix of extracellular polymeric substance (EPS). This polymeric conglomeration is generally composed of extracellular DNA, proteins, and polysaccharides.

Biofilm can be found in water distribution systems where the processed water constantly flows or loops through a network of pipes and valves. Inherent in these distribution systems are a series of turns with elbows and other configurations that impede the flow of water. It is at these locations where the water slows down that cells can adhere to the surface of the pipe and begins the process of developing a biofilm.

Biofilm development is a key concern with in-house water systems. Once validation is complete, the system and its filters should be constantly monitored and maintained. The system's use of ultrafilters or charge-modified filters minimizes endotoxin levels by controlling the introduction of free endotoxins and microorganisms in the feed water and minimizing microbial proliferation in the system.

Producing Water-for-Injection In-House
The pharmaceutical and biopharmaceutical 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. To ensure that the system is meeting these standards, routine QC testing and monitoring must be in place.

These are some common characteristics of in-house water systems:

- Water for Injection is usually stored in a continuously circulating system and 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 and the proliferation of biofilms.
- 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.
- To obtain the required quality of WFI, distillation or reverse osmosis filtration must be used for the final step.

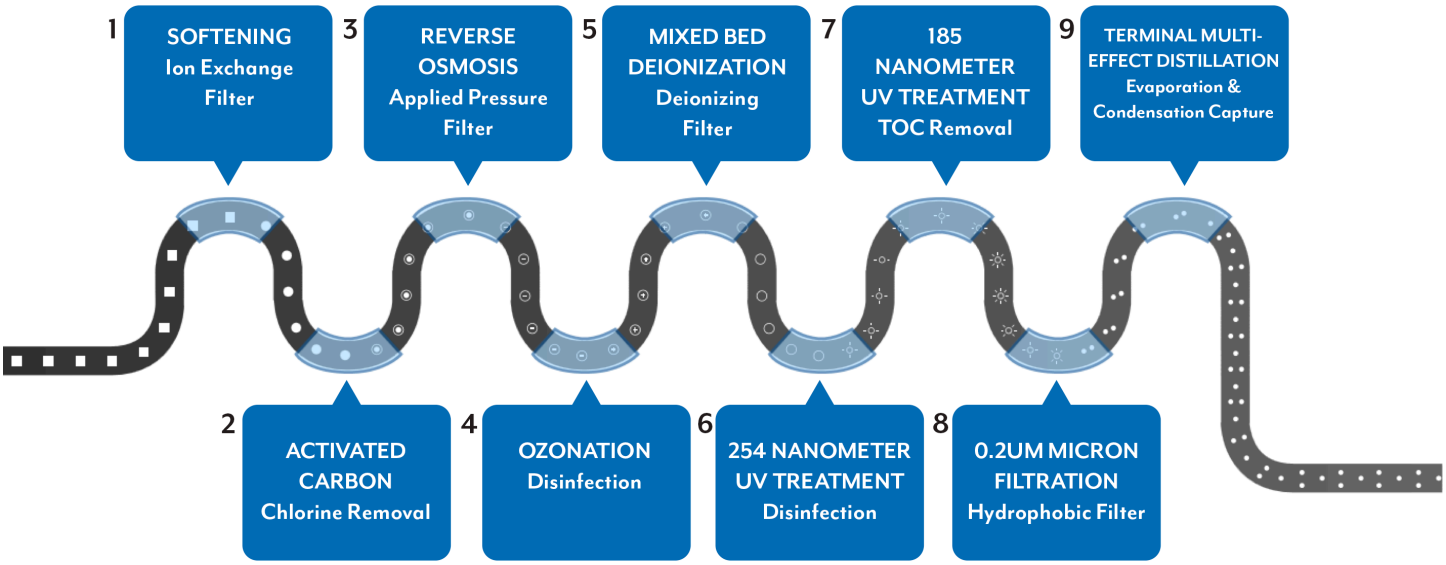
Water for Injection Systems
Water purification systems come in a wide range of configurations. Most all are custom designed to account for the source water as well as the final product needed for the application. The unit shown here can produce either purified water or WFI.

Purification Process for High Purity Water
To reach the desired level of water purity, a series of treatment steps are required. The source water must also be taken into consideration when designing the system. Many systems will be somewhat unique based on the quality of the source water.

The schematic below, courtesy of RMBIO, portrays the series of treatment steps employed to produce WFI quality water. RMBio is a commercial supplier of multiple grades of high purity water. With this process, they produce both sterile and non-sterile USP water products.

These are treatment steps that RMBIO utilizes in its nine-step proprietary purification system:

- Softening
- Activated carbon/chlorine removal
- Reverse osmosis
- Ozonation
- Deionization
- UV treatment
- TOC removal
- Ultrafiltration
- Distillation



Does Your Company Outsource Water?

For the Laboratory:

- Most of the non-monographed analytical waters described above are commercially available. These are vital to labs that do not have a water purification system sufficient enough to produce the level of purity needed.
- It is possible to produce the required high quality water with in-lab systems. However, it is imperative that the system is routinely monitored, including filter changes and performing timely maintenance.

For Production or Scale-up:

- One might assume that the decision to outsource water verses producing from an in-house water system is always an economic one. Often that is true but many organizations purchase water because they require a high level of consistency, documentation, or traceability for waters they use for production, R&D or quality control.
- As a general rule, larger organizations with large volume production needs may produce water in-house to meet the purity requirements of their applications. For economic reasons, companies with lower volume requirements will typically outsource their high purity water. Outsourcing is a good option that will deliver the quality parameters required for the application.
- Large scale water systems for production applications are quite expensive to acquire, install, validate, and maintain. In addition, the water produced must undergo ongoing QC testing to ensure that the system is producing the quality of water needed for their specific process. All procedures for sampling and testing must follow an established set of SOPs that have been developed during the validation process.

Benefits of Outsourcing:

- Outsourcing high purity water can make good economic sense for most small to medium sized manufacturing sites especially when compared to the cost of owning an in-house system.
- For facilities in transition or growth phases, outsourcing bulk water can offer everything an in-house system provides without making a significant financial impact.
- Finding a supplier of the packaged bulk water who meets industry standards and compendial specifications is not difficult. These sources will provide the consistency, documentation, and traceability that is required for the process.

Closing Remarks

There are clearly defined specifications for a wide array of high purity water grades.

Selecting the correct grade is generally not difficult but the right questions must be asked:

- Is the water for scale up/production (bulk) or analytical applications?
- If for scale up/production, are the specs defined by USP or EP?
- Is the end product parenteral or non-parenteral (sterile or non-sterile)?
- For analytical applications the specs are defined by ASTM or USP. (These procedures generally specify the grade of water required.)

Once the grade of water is determined, does the site have capability and capacity to produce the water on-site? If so, are all the requirements for validation, maintenance, QC testing, and documentation in place? If the current system can't produce the purity level or volume needed for a long term project, then decisions must be made. If the choice is made to upgrade the facilities, the investment of time along with the cost of equipment, its validation, and maintenance must be made.

For organizations in a start-up or growth phases, outsourcing bulk water can offer everything an in-house system provides until the in-house system is fully operational.

If outsourcing water is your best option at this stage, you can be assured that most commercial high purity water producers will provide the consistency, documentation, and traceability that the intended process requires.

It was mentioned earlier that "all pure water is not the same." To be fair, a lot of high purity water is similar and may be appropriate for almost any application. A batch of water from a high purity system can be labeled as a number of different grades because it will be tested to assure that it will meet the specifications of a number of different grades.

Some commercial water producing facilities only produce one top-of-the-line water then test it to meet the specifications of any number of different grades. Then each production lot of water comes with its own set of specifications, labeling and a certificate of analysis.

If you outsource water, no matter what the grade, you will want to purchase your water from a company that produces WFI quality water. That brand will be the best water you can buy.

There are literally thousands of scientific applications currently encountered in FDA-monitored facilities. With many high purity water products on the market today it is likely that outsourcing is an excellent option for many of these applications.

What grade of water does your organization require?

Within a single company there could be multiple processes requiring a range of water grades. Below are the various grades that are available from Spectrum Chemical.

Analytical Water Applications:

- HPLC
- LC-MS
- Low-organic water – organic analysis
- Ultratrace water – elemental analysis

Routine Laboratory Applications:

- ACS reagent grade water
- ASTM Type I, II, III, or IV water

Biological Laboratory Applications:

- Molecular biology grade water
- Cell culture grade water

R&D through Manufacturing Applications:

FDA-monitored processes will normally dictate what grade of water is required. In in which where the end-user is not sure, contact Spectrum Chemical and consult with our technical specialists on your high purity water needs.

These packaged products for manufacturing and R&D are available commercially:

- USP purified water
- USP sterile purified water
- USP sterile water for injection
- USP/EP sterile water for injection
- USP sterile water for irrigation

Where Does All This Water Go?

It would take a few more white papers to describe even a portion of how high purity water might be used in FDA-monitored facilities.

A fair amount of this water goes into making buffered salt solutions, saline, or custom process solutions for manufacturing applications such as:

- Purification and chromatography buffers
- Cell and tissue processing solutions
- Diagnostic manufacturing
- Medical device processing
- Cell culture media and feed solutions

Solutions like this typically start with compendial grade water and utilize compendial grade ingredients to prepare the solution.

In sum, all "pure" water is not the same and appropriate for every application. The final product will dictate the type of water that is required from the start.

A typical bioprocessing suite uses large volumes of pure water for each production run

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References:
http://www.pharmacopeia.cn/v29240/usp29nf24s0_c1231.html • http://textbookofbacteriology.net/endotoxin.html