

Why Quality is Critical:

Packaged USP Purified Water for Pharmaceutical Use



CHATA
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Quality to an Exacting Degree

If you manufacture or test products for the various healthcare markets, you fully understand the critical nature of the water employed. Widespread in pharmaceutical and diagnostic preparations and typically the major component, water is also the raw material that is given the most scrutiny by scientists, engineers and regulators alike. Water used for pharmaceutical purposes, whether for laboratory or manufacturing purposes, is saddled with an understandably exacting degree of purity and safety to ensure the public health. Purified Water, as defined in United States Pharmacopeia will meet this burden; however, the production and use of such water is an on-going effort to maintain proper engineering and testing controls.

The Concise Requirements in the USP

The USP <36> monograph for Purified Water is elegant in its brevity, but that elegance comes at the price of systematic complexity. In past years, the USP monograph for Purified Water has undergone significant changes, especially when compared to other countries. Figure 1 shows the compendia test requirements for Purified Water according to the official US, European and Japanese monographs.

Figure 1
Compendia Requirements for Purified Water

Requirement	USP	Ph. Eur.	JP
Conductivity	≤1.3 μS/cm @ 25°C	< 1.1 μS/cm @ 20°C	-
Total Organic Carbon	< 500 ppb	< 500 ppb	-
Nitrates	-	< 0.2ppm	No color developed
Chloride	-	No color developed	No color developed
Sulphate	-	No color developed	No color developed
Ammonia	-	< 0.2ppm	< 0.05 mg/L
Heavy Metals	-	< 0.1 ppm	No color developed
Oxidizable Substances	-	No color developed	No color developed
Bacterial Endotoxins	-	< 0.25 IU/mL	< 0.25 EU/mL
Acidity/alkalinity	-	No color developed	No color developed
Residue on Evaporation	-	< 0.001%	< 1mg / 500mL
Total Bacteria Count	-	<100 cfu/mL	-
Aluminum	-	< 10 ppb	-
Calcium / Magnesium	-	Blue color developed	-
Total Solids	-	-	< 10ppm
pH	-	-	5 to 7
Nitrites	-	-	No color developed

The concise requirements in the USP spring from a modern concept that water for pharmaceutical use, as produced by a suitable system, cannot rely on spot testing as a substitute for proper system design, validation, and operation. Analyst driven assay results are typically available only after the water has been used, so the newer requirements are more control-based rather than release-based. A properly engineered Purified Water generator and distribution loop will deliver quality water to meet these requirements when adequately maintained; however, validated systems require continual and intensive support to assure the water produced will meet these stringent specifications on demand.

Is the Capital Investment Worth It?

For many companies, these on-going investments in capital, personnel and QA/QC efforts will likely not result in a reasonable return based on their volume needs. Even with this commitment to design and acute awareness, water systems are required to be taken off-line for periodic maintenance or sanitization, or a temporary water drop is immediately required in an inconvenient location. The common solution is to bank the water into secondary storage containers that can be transported, if necessary, but this activity confronts systems engineers and QA managers alike with yet another layer of design and validation complexity to demonstrate both chemical and microbiological purity without interaction from the secondary container or package.

Using Third Party Vendors

Both large and small health care product companies have turned to third-party vendors for their water needs, both as an outsourcing activity and in crisis; however, vigilance is required to engage the selected vendor so your water requirements and expectations are met. Current outsourcing opportunities for Purified Water, USP, are limited to small glass or plastic packages that can only meet the regulatory requirements at



the time of fill. Remember, as the buyer and the one with the ultimate responsibility for your product's

FIGURE 2

Some Suggested Areas to Investigate with New Purified Water Vendors

1. Is the system design and validations adequate for the product produced?

There are limited USP testing requirements, which place more emphasis on system control. Also, Water for Injection and Purified Water are NOT interchangeable. If you need WFI, then you must use WFI.

2. Are operational controls and cGMP compliance in a demonstrated state for packaged water?

The typical needs of controlled products should be available, such as production records and Certificates of Analyses. Simply pulling water off an operational system loop is not enough. In-line controls do not transfer to packaged product.

3. What are the Lot Traceability control methodologies?

In a recall situation, you will have to demonstrate the water met specifications at the time of use. Many vendors will state "at the time of filling", especially Total Organic Carbon. Consider also if an expiration date is provided and what that date really means. The date must be justified with adequately developed stability studies so you know the water quality when you use the water.

4. Do the secondary package construction, composition and use meet the needs of your facility?

Transferring clean water into dirty containers will just compound your problems. Package contamination is a likely source of batch failure and this can come in the form of either chemical or microbiological exposure. Purified Water is devoid of buffering ions and its leaching abilities are well known.

quality, you must be assured that actual Purified Water, USP is being used, not just purchased.

The Total Organic Carbon requirements of Purified Water, USP are less than 500ppb, which is a reasonable specification for dynamic state systems but difficult to maintain in static or packaged state. Leachates from the package or microbial contamination will obviously contribute to the TOC over time and must be understood by either the manufacture or user. Consideration must also be given on how the purchased water will be used in the manufacturing plant or

laboratory. For example, pouring 1L glass bottles into a 1,200L reactor is both a safety and labor mischance that could have been avoided with planning.

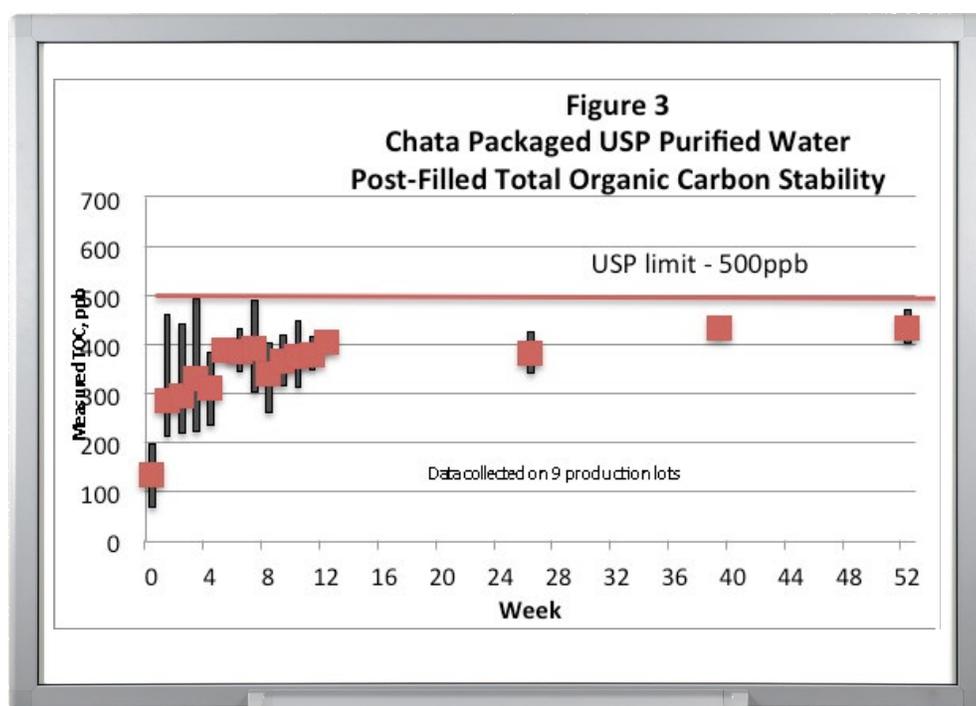
For the past 12 years, Chata Biosystems has been developing and commercializing low extractable flexible packaging primarily for use with mobile phases, dissolution media and elution buffer that protects the fluids from environmental contamination with a convenient use profile. Utilizing the unique CHEM-NECT® flexible packaging system, Chata can provide discerning clients with expiration-dated water from a

continually validated system that will meet or exceed internal requirements with a minimal investment. Users simply connect a peristaltic pump to the drum connector and use the water via a closed loop. Chata USP Purified Water can be a trusted solution when a water system is undergoing maintenance and unable to provide high purity water in the quantities necessary, or when Management is looking for ways to decrease internal overhead costs associated with maintaining a water system.

As suggested earlier, most well engineered systems will produce Purified Water, USP at the time of package fill, but the patent protected CHEM-NECT® flexible packaging system will maintain this chemical and microbiological purity after fill, during shipping and on the shelf. Real time stability data for Chata Biosystems USP Purified Water were studied over multiple lots to demonstrate the integrity of the CHEM-NECT® flexible packaging system and its ability to maintain a closed environment. All water was generated by Chata's validated

reverse osmosis system and distribution loops. The water was sterile filtered under cGMPs into 200L CHEM-NECT® bags placed inside plastic drums using Tygoprene tubing and polypropylene connectors then stored at ambient warehouse temperatures for the duration of the study. At defined time points, aliquots were aseptically removed from the drums and evaluated for the stability indicating parameters of USP <645> Total Organic Carbon, USP<643> Conductivity, and USP <71> Sterility.

Figure 3 shows the range of TOC readings on 9 discreet production lots through 12 months. The data displays a rising trend after fill that plateaus in the first 3 months but never rises above the 500ppb upper limit for Purified Water, USP. In fact, no TOC measurement was out of



specification, with the range of TOC values between 68ppb and 492ppb for the 52 weeks of study. USP Conductivity and USP Sterility also all remained within limits for all lots tested. This stability data affirms that USP Purified Water produced by Chata and filled into 200L CHEM-NECT® bags remains within USP specifications for Purified Water for up to 12 months when stored at ambient temperatures of 4° - 40°C.



The use of USP Purified Water from Chata Biosystems can be a powerful tool in your facility to ensure an adequate supply of water, control costs and improve efficiencies. The ability to mobilize water where you need it and when you need it, and at a fraction of the cost and hassles of maintaining a high purity water system, allows production facilities and testing laboratories flexibility and control not previously encountered. The establishment of an expiration date provides assurances of water quality not only at the time of fill but at the time of use.

Chata Biosystems produces premixed laboratory and manufacturing reagents and buffers for critical industries. All products are produced under cGMPs with its Quality Systems certified to ISO 9001:2008 and ISO 13485:2003.

Chata excels in regulated production of unique formulations packaged in patented systems to protect the solutions and user during use. For more information, visit www.chatasolutions.com.