Modifications to the Purified Water Storage and Distribution System Polytechnic University of Puerto Rico

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Abstract *— The Purified Water is identified to play an integral role in manufacturing operations. Careful considerations and good manufacturing practices must take place in order to minimize contamination and bacterial load. It is vital for the quality of the processes and operations that the Purified Water system operates in a consistent manner, providing a high quality product. Automatic valve control for dispensing Purified Water will provide a higher level of assurance that quality is maintained consistently.*

Key Terms *— Pharmaceutical, Purified Water, Qualification, Total Organic Carbon.*

INTRODUCTION

A Purified Water (PW) system is a critical system that impacts the processes and operations in a pharmaceutical manufacturing plant. Raw water incoming from the "Autoridad de Acueductos y Alcantarillados" (AAA) is unfit and contaminated with minerals and chemicals to be used as-is. Therefore, additional steps and water treatment must take place in order to be able to treat this raw water for manufacturing processes.

There are many methods of treating the raw water. Its selection will depend greatly on the demand that the system will need to deliver. One of the most common ways of water treatment is by Water Softener and Reverse Osmosis (RO).

"Purified Water" as established by the United States Pharmacopoeia (USP) Regulations is one that:

- Is obtained from water complying with the "United States (US) Environmental Protection Agency (EPA) National Primary Drinking Water Regulations" (or comparable Europe Union (EU), Japan (JP) regulations) [Refer to Table 1].
- Contains no added substance.
- Is obtained by a suitable process.
- Meets the requirements for Water Conductivity.
- Meets the requirements for Total Organic Carbon (TOC).

Table 1
Microbial and Chemical Acceptance Criteria for Purified Water

Test	Chemical	
Description	Clear and Colorless liquid, no odor	
Conductivity	No more than 1.3µS/cm @ 25°C	
Nitrates	No more than 0.2 ppm	
Heavy Metals	No more than 0.1 ppm	
Total Organic Carbon (TOC)	*Alert Limit*	*Action Limit*
	≥ 200 ppb	≥ 300 ppb
Test	Microbial	
Total Aerobic Count	No more than 100 cfu/mL	
	Alert Limit	*Action Limit*
	≥25 cfu/mL	≥50 cfu/mL

Project Description

PW is a critical system in a manufacturing process. Current operations in many manufacturing plants rely on operators to ensure water meets acceptable quality parameters due to its design. Manufacturing plants that do not have an automated process of dispensing PW may run into difficulties and problems later in the supply chain. Using PW that does not meet acceptable quality parameters will result in rejected lots and non-compliance with the Federal Drug Administration (FDA) regulations. The manufacturing plant has identified the following critical situations:

- The pump suffers cavitation damage when the flow from the storage tank is not sufficient.

There is no automatic shutdown fail safe for the pump to ensure adequate operation.

- During ozone sanitization process, there is no automatic lockout on the points of use (POUs) for the PW distribution system. This is only covered by a Quality Hold Status tag that is placed on the POUs prior to Sanitization.
- PW dispensing is not controlled automatically; therefore there is no assurance that the PW that is being dispensed meets acceptable quality parameters such as Conductivity, TOC and Dissolved Ozone (DO_3) levels.
- There is no fail-safe to close out the POU and maintain it closed due to failures in the system.

Project Objectives

The PW Storage and Distribution loop that supports the manufacturing operations will undergo several modifications. These modifications will enhance and upgrade current operations.

The upgrades of the PW System consist of the following modifications:

- It will provide automatic control of the POU valves so that the automatic valves will close, if open or remain closed in the event that the distribution pump fails or shuts off.
- It will ensure that acceptable DO_3 concentration is maintained throughout the system during the ozone sanitization process as measured at the return line of the storage tank.
- Provide automatic operation of five (5) purified water POUs to ensure that the dispensing of the PW only occurs when suitable operating and water quality attributes/conditions are within acceptable limits.
- Ensure automatic shutdown of the existing distribution centrifugal pump to protect pump from cavitation damage on the event of any low flow condition from the PW storage tank.
- Install new spray balls in the interior of the PW storage tank to ensure that the upper head and interior side walls of the tank are kept continuously wetted during regular operation. This prevents stagnant water and eliminates the possibility of bacteria formation.

Project Contributions

Quality - The new automatic system for PW dispensing will provide a higher grade of assurance that the PW will meet consistently acceptable quality parameters for manufacturing. The colony formation units (cfu) will be lower due to an improvement in the sanitization procedures.

Time - Time will be greatly reduced for opening and closing Points of Use. Time it takes to ensure that the PW are within acceptable parameters TOC and Conductivity through inline monitoring at the PW system room will also be reduced.

Costs - Due to a higher degree of monitoring, costs related to the repair and maintenance of the PW system will be lower. Costs related to the rejection of lots due to using PW for manufacturing that do not meet acceptable quality parameters. The improvement of the sanitization procedure ensures that the system will have a lower rate of microbial cfus.

Safety - Operators that are in charge of dispensing and transporting the PW across the different manufacturing areas will be safer with the new automatic valve dispensing system. The interlock with the new automatic valves and Programmable Logic Controller (PLC) that does not allow the valves to open give a higher assurance that it will not permit DO_3 to reach manufacturing areas.

BACKGROUND

The water treatment equipment removes unwanted impurities from potable water and produces high quality purified water that is stored, preserved and distributed to the points of use located throughout the manufacturing area. Conductivity and DO_3 analyzers and sensors monitor the process to assure that PW consistently meets established requirements.

The system is fed from municipal potable water supply. The feed water is pretreated with a duplex parallel water softener unit and then fed to the Pre-treatment Water Tank. The pre-treated water is then processed using Reverse Osmosis (RO), electro-deionization (EDI), a 185 nanometer sterilizing

ultraviolet (UV) Light at the EDI output line and a mixed bed deionization unit to polish water to 18MΩ. One 0.2 microns post filter is installed between the mixed bed deionization to purify it and then distribute it to the PW Distribution Tank System.

The make-up capacity of the PW System is approximately 12 gallons per minute (GPM) and supplies water to the PW Distribution Tank System. The distribution tank are a continuous recirculation system in which the PW is pumped from the purified water tank through the piping to the POUs and back to the tanks. It consist of the purified water tanks, purified water pumps, DO_3 sensors, TOC / Conductivity analyzer, vent filters, vent ozone decomposer, sanitary stainless steel piping, ozone generators and ozone destruction UV lights.

UV lights are effective in inhibiting microbial growth but are only effective where the light is present. UV lights are usually used before a unit operation to minimize the microbial growth in the unit operation by controlling the microbial counts in the feed water.

System Description

The PW Storage and Distribution system consist of two (2) storage tanks with separate distribution loops to feed the manufacturing operation for the X and Y manufacturing areas. Each PW storage tank is fed from a common PW Generation System [1]. Both PW loops are currently in operation and are qualified. Although the purified water storage and distribution system consist of two (2) distribution loops, this system description denotes the X system.

The X PW Storage and Distribution System consists of a 250 gallons 316L Stainless Steel Tank rated at 14.0 psi and a single sanitary centrifugal pump provided with a 45 degree discharge orientation and a ½" casing drain port. A UV light assembly is provided at the discharge side of the distribution pump for the ozone destruction [2]. A single non-heated 10 inch, 0.2 micron sanitary cartridge vent filter is supplied to the tank to allow breathing during filling and draining operations [3]. The X PW storage tank is supplied with a spray ball [4]. Instrumentation is provided to monitor, control and alarm the tank water level. Also to monitor and alarm conductivity, TOC, DO_3 and rupture disc failure. Local pressure indicators are supplied at the discharge side of the pump and at the return loop piping prior to entering the tank. Three (3) sample points are provided throughout the distribution piping, upstream and downstream of the UV Light, in order to allow for sampling operations of the PW.

The PW Storage and Distribution system is sanitized on a monthly basis with ozone [5]. The system sanitizes the PW storage tank and distribution loop by injecting ozone into the storage tank and then distributing throughout the loop. Injection of the ozone into the PW storage tank is done subsurface by introducing the ozone rich water stream, into the Purified Water tank, through a dip tube at a level below the water surface. Instrumentation to measure DO_3 is provided for the PW storage tank right before entering the UV Light and for the supply side of the distribution loop right after the UV Light. When the DO_3 sensor in the supply side of the distribution loop piping measures higher levels than the low ozone set point a timer will start and measure the length of the sanitization phase. During the sanitization phase, the DO_3 concentration is measured in the distribution loop supply piping to determine that acceptable concentration of dissolved oxygen is being maintained and supplied to the entire distribution loop for the whole duration of the sanitization phase [6]. Upon completion of the PW system sanitization the remaining ozone is destroyed by means of UV lights supplied at the discharge side of the distribution pump.

The ozone is generated by an Ozonia Triogen, corona type ozone generator. A static mixer is supplied in order to effectively mix the ozone with a side stream of PW before entering the PW Tank. Since ozonized water will result in ozone gas accumulating in the tank's head space, as water is added to the system, it will result in air, oxygen and ozone being forced out of the tank through the vent filter. Ozone outgassing shall be handled by thermal

ozone Destruct Unit connected to the vent line from the PW Storage Tank.

The X PW Storage tank is equipped with an ambient ozone monitoring sensor, in order to detect possible leaks of ozone out to the room's atmosphere. In the event of a leak of ozone is detected, the system will automatically shut off the ozone generator and alarm the operator of a possible leak of ozone out to the room's environment.

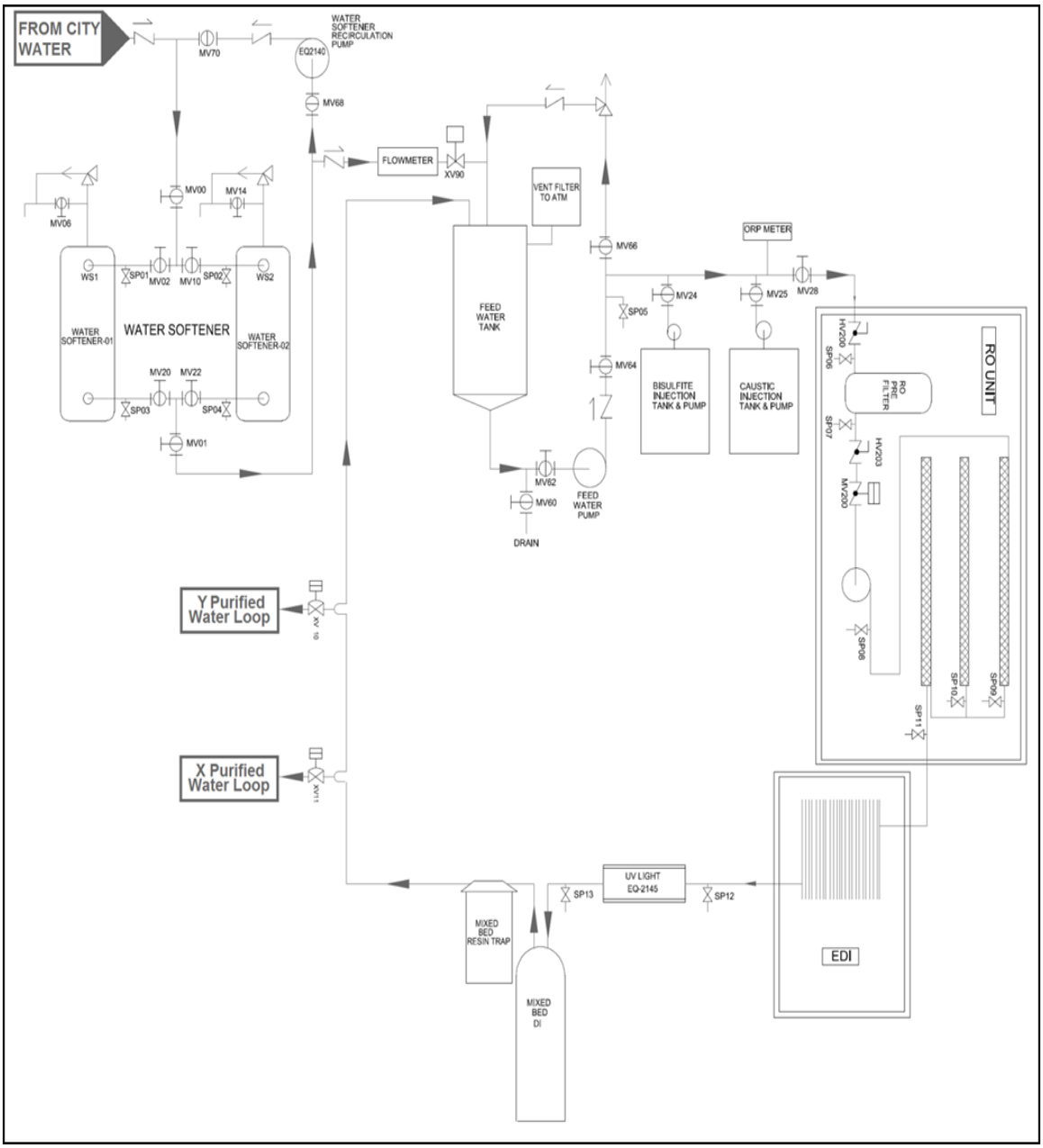

Figure 1
Water Generation System Diagram

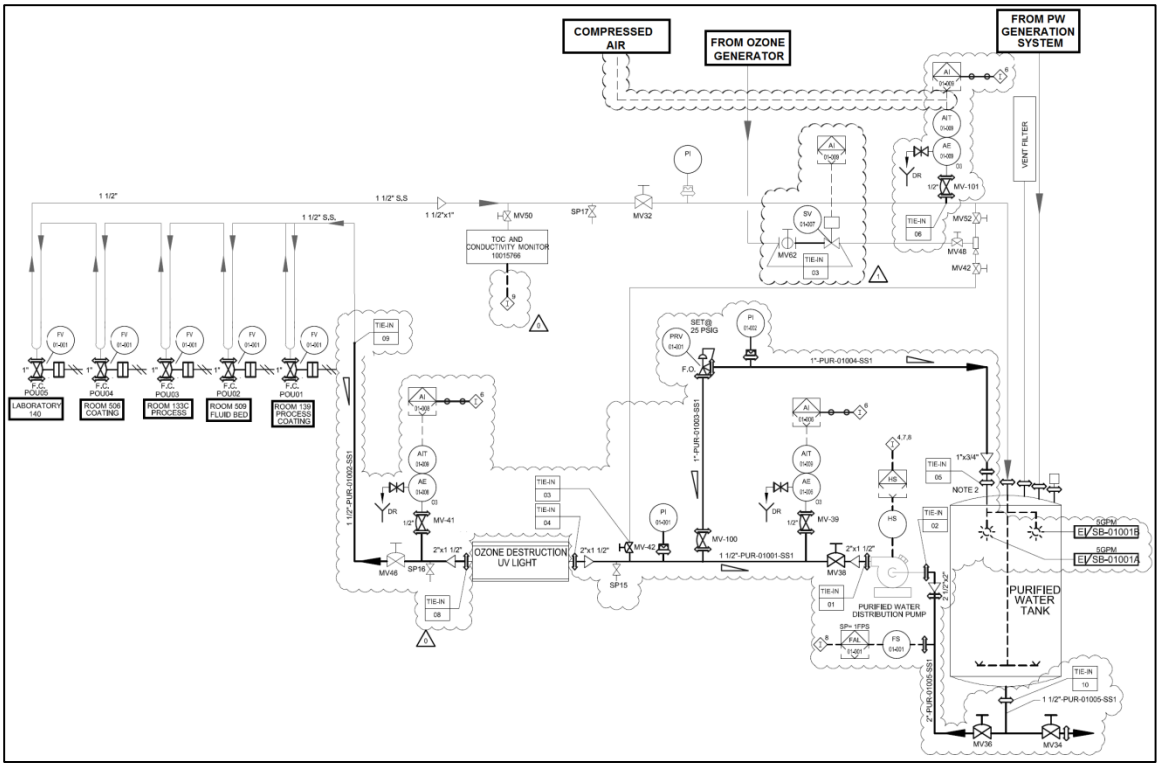

Figure 2
X Purified Water Loop Diagram

PROJECT METHODOLOGY

The manufacturing plant is currently in full operation. Downtime of a critical system such as PW will affect greatly in the production. Careful planning must be achieved in order to minimize downtime and reduce costs. The best approach to the modification of the PW Storage and Distribution System is by phases. All activities that can be performed without having a direct impact to the system will be identified, such as they can be executed in advanced without having a system downtime.

Phase 1 – Beginning of Documentation

This phase is characterized by the development of documentation required for the construction of the modification to the PW Storage and Distribution System. The User Requirement Specifications (URS) is assumed to have been developed, routed, approved and sent to the contractor in order for them to develop a design by the time Phase 1 starts.

Concurrently, while the contractor develops their Design Specification (DS) with the URS, the manufacturing plant's Technical Services (TS) develops the Validation Master Plan (VMP) in order to capture all of the activities needed to successfully qualify the modifications to the PW system. While the Validation Master Plan (VMP) is being reviewed and approved, the Installation and Operational Qualification (IOQ) protocol will be developed.

The DS needs to be received by the manufacturing plant and approved by the Department directors of which this project will impact on. Also, when the VMP is reviewed and approved by the same Department directors, Phase 2 can begin.

Phase 2 – Construction and Installation Qualification Execution

This phase is characterized by the construction of the modifications to the PW Storage and Distribution System. Also, while the construction is in progress, the Installation Qualification (IQ) part of the IOQ can be executed concurrently in order to

maximize efficiency and reduce downtime. The Operational Qualification (OQ) can only be executed once the construction has finished and calibration of the equipment's components has been performed [7].

During the construction, the PW Storage and Distribution System will not be in shutdown until all of the activities that do not impact the system directly have been performed. The five (5) POU panels will be installed in each room and their conduit wire will be taken from each room towards the Mechanical Room. Mechanical components that need to be installed in the X PW Loop such as Flow Switch, Pressure Reducing Valve, Stainless Steel Piping, etc. will be in site and available where it is going to be installed prior to shut down.

Once all of these activities have been performed, the shutdown will be scheduled with the manufacturing operations in order to minimize the impact on production and other arrangements can be made in order to supply PW where needed. After all of the installation of the new equipment has performed and the program of the Human Machine Interface (HMI) and the PLC has been updated to cover all of these changes, the system will start up again.

Phase 3 – Calibration and Operational Qualification Execution

After the system has been started up, the calibration of the components such as DO_3 sensors, TOC and Conductivity Analyzer/Transmitter, Chart Recorders, etc. need to take place. When these activities have been performed, the OQ execution can begin.

During the execution of the OQ, the interlock of the system and the sequence of operations are challenged. The sanitization procedure with DO_3 is then performed and tested. After these three (3) tasks have been performed, the Microbiology and Chemistry Department begin their ten (10) consecutive day sampling as per the manufacturing plant Standard Operating Procedures (SOPs).

Phase 4 – Final Documentation

After the IOQ has been successfully executed and its Final Report developed and approved, TS can now close documentation activities by generating a Final Report for the VMP [8].

The Final Report for the VMP must be approved by the impacted departments and Quality Assurance (QA). When approved, the PW system is considered to be qualified and ready to begin supplying PW to the manufacturing plant.

RESULTS AND DISCUSSION

It was determined during the execution of the operational part of the IOQ that the valve selection for the POUs was not ideal. The volumetric flow of the POU actuator valves could not be restricted and was noted to exceed the required parameters. Originally, the operator could control the volumetric flow with the position of the manual valves. The Engineering Department was notified immediately and issued a Work Order (WO) to purchase an optional part for all the POU valves that would permit them to limit opening of the actuator valve. The Automation team was notified of this modification to ensure that the limit switches of the valves did not affect the programming and logical sequence.

During the execution of the sequence of operation, the Automation team had to modify the programming to correct a design flaw that would permit the PLC to feedback once the Open button was pressed and therefore the valve would not close automatically with the preset timer.

The ten (10) consecutive day microbial and chemical sampling was completed successfully. Refer to Table 2 and Table 3 for the results of microbial sampling. All samples collected complied with the nitrates test and were a clear colorless liquid with no odor. All samples were within the established parameters set by the manufacturing plant's specifications and requirements for PW (Refer to Table 1).

The PW POUs now only dispense water when all quality parameters are within acceptable limits.

Table 2
Microbiology Sampling Results

Total Aerobic Count (No more than 100 cfu/mL)										
Day	POU-01		POU-02		POU-03		POU-04		POU-05	
	SMA	R2A	SMA	R2A	SMA	R2A	SMA	R2A	SMA	R2A
1	1	1	0	3	0	2	8	12	25	3
2	0	0	0	0	0	0	8	2	5	4
3	0	0	2	1	0	0	5	7	7	5
4	3	6	2	1	0	0	12	5	0	0
5	2	0	3	5	0	0	2	5	8	5
6	1	1	12	6	0	0	15	9	11	15
7	2	2	4	9	1	1	12	14	12	8
8	13	9	11	13	1	1	18	8	14	19
9	2	0	24	17	0	4	12	28	35	32
10	17	18	19	21	2	3	37	27	17	26

SMA – Standard Methods Agar culture medium.
R2A – Reasoner's 2A culture medium.

Table 3
Total Organic Carbon (TOC) and Conductivity Sampling Results

Day	TOC (ppb) No more than 300ppb	Conductivity (µS/cm) No more than 1.3 µS/cm @ 25 °C
1	12.80	0.60
2	11.40	0.65
3	11.40	0.63
4	11.60	0.63
5	11.40	0.57
6	10.80	0.63
7	11.30	0.64
8	11.50	0.61
9	10.20	0.64
10	40.60	0.53

The pump shuts down when the flow is insufficient, therefore ensures that it won't suffer from cavitation damage.

The modification to the sanitization procedure now ensures that the entire PW distribution loop reaches and maintains the established DO_3 concentration levels through the sanitization sequence. This gives a higher level of assurance that the PW distribution loop is sanitized effectively.

It was confirmed during the execution of the operational qualification that the entire surface of the PW storage tank is maintained wet; this ensures that the bacterial formation is minimized on the surfaces of the tank.

All documentation was closed successfully at the end of the project yet there were some delays in the review and approval of the reports and documents. These delays did not impact the project schedule as they were not in the critical path of the project and were managed successfully.

CONCLUSIONS

The project was completed satisfactorily; from a construction and documentation perspective. The PW system is qualified and ready to supply the manufacturing plant's operations.

The new modifications to the PW system facilitate the operations in the manufacturing plant. It also provides a higher level of assurance that the PW that is used in operations will be within acceptable quality parameters.

The ten (10) consecutive days sampling results were all within acceptable quality parameters. Although, some of the POU were at the alert level on the microbial results at the 9^{th} and 10^{th} day. Refer to Table 1 and Table 2. The TOC and conductivity (Refer to Table 3) were all below the established manufacturing plant parameters (Refer to Table 1).

The SOPs regarding the usage of the PW and the sanitization procedures were updated to ensure a safe

usage of the system. Departments and personnel that were impacted by these modifications and these updates in the SOPs were retrained in order to make the SOPs effective [8].

The selection of the model of POU actuator valve was not ideal, even though it met with all the requirements stipulated by the manufacturing plant. It was recommended to make a modification or to change the model of the actuator valves in order to have the ability of modulating the amount of volumetric flow the valve would dispense.

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