

A Compilation of WHO GMP Audit Points

Collected from WHOPIR of 28 companies
Part II of VIII

Current article – Part II Water Systems

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Water Purification System:

- PW was continuously circulated at ambient temperature which was controlled by a flow meter and jacketed cooling of the main tank. Conductivity was controlled on line at two points after the PW storage tank and after the recirculation loop on return to the tank and water was automatically dumped to drain if limits were exceeded.
- Performance Qualification and Operational Qualification of the PW system was carried out in three phases. Phase I was for 14 days, phase II was also for 14 days and phase III was 11 months.
- UV lamp working hours and intensity was controlled continuously. The system was sanitized weekly by heating and sanitization and maintenance was recorded. Recirculation of the PW was through PVDF pipe work which was FDA approved and the certificate of conformity (PVDF) for PW system distribution lines was reviewed.
- **A schematic drawing was available which was identical to the one in the Site Master File.** The pipe work was SS304 for pre-treatment modules and SS316 for the purification stages. Pipe welds were electro-polished and certified as such.
- Water was filtered, dechlorinated and softened in the conventional manner. Purification was achieved using a combination of micro-filtration (5.0 micron), UV irradiation, RO and EDI.
- A further UV irradiation step was employed at the start of the loop. The UV lamp was monitored for lamp life (max 5.6K hours). The RO units had a working flow range of 1.8 to 2.2 m³/hr.
- Alert limited and action limits were subsequently incorporated in a new SOP on cleaning of RO membranes and EDI I purified water system.
- SOP "Procedure for Operation of the Purified Water Distribution".
- SOP "Procedure for operation of Purified water distribution loop".
- Welding records were available. Pipelines were connected by using orbital welding. Print outs of orbital welding machine were available and presented to the inspectors Baroscopic welding was recorded on CD.
- Purified water was monitored by taking samples from the points of use in the loop on a daily basis following a routine set out in an authorized SOP. The sampling plan allowed for each outlet to be checked each week. Results routinely met the specification for purified water for pharmaceutical use.
- The water produced had a conductivity of less than 1.0 µS/cm. The storage tank was fitted with a 0.2-micron hydrophobic vent filter. Cold water circulated through the loop with 16 take off points. Dead legs were less than 2-pipe diameters.
- Flow rates were sufficiently high to prevent the buildup of bio film.
- TOC testing has to perform routinely.
- The system was sanitised with 1% hydrogen peroxide solution as per schedule and records were maintained. The storage tanks were cleaned by draining down before manual Cleaning.
- Qualification documentation was available for the extension of the water loop; documents about design, installation and system start were included.
- For complete hot water sanitization of the system (including feed line) an occasional flexible connection was implemented in the system. A thermometer in the return water loop allowed correct measurement of sanitization temperature.
- PW was continuously circulated at ambient temperature which was controlled by a flow meter and jacketed cooling of the main tank.
- Conductivity was controlled on line at two points after the PW storage tank, and after the recirculation loop on return to the tank water was automatically dumped to drain if limits were

- exceeded.
- UV lamp working hours and intensity was controlled continuously.
- The system was sanitized weekly by heating and sanitization and maintenance was recorded.
- Recirculation of the PW was through PVDF pipe work which was FDA approved and the certificate of conformity (PVDF) for PW system distribution lines was reviewed.
- The inspection focused on the design of the system, verification of components installed including spray balls, MOC, PW tank, loop, valves, UV treatment, slope, sensors, dead legs, daily monitoring, and sanitization - specifications, procedures, and records
- The schematic drawing for the purified water system was discussed and questions were raised regarding the design, maintenance, validation and monitoring of the system.
- PW system was continuously monitored by weekly sampling and MB & chemical Analysis.
- Sampling schedule indicating sampling points were available.
- URS, DQ, IQ, OQ and PQ protocol/reports were available. Water storage tank and loops were made from SS 316L. Orbital welding technique was used for the joints, welding Quality was checked by boroscopy. Four boroscopy photographs were available and were presented. Welding reports, welding clearance format and welder's certificate were Available.
- SOP "Water sampling technique for MB analysis and chemical analysis" was reviewed and found to be satisfactory.
- **The PPM program and monthly records for particular year, for the water system, should be prepared.**
- Resanitising the water loop ahead of schedule to accommodate a weekend shut down.
- Purified water was produced by a double pass RO-EDI/ED-UF system. The distribution system of each system was under continuous cold re-circulation through an electro-polished SS 316 loop.
- Raw water was pumped through PVC pipe work to the softening and chlorination modules. There after pipe work consisted of 316 SS.
- All pipe welds were electro-polished and certified.
- Purification of water is first through RO, followed by EDI and UV irradiation TOC was monitored on line.
- Sensors are arranged to detect OOS and could stop and recirculation the water.
- Routine production gave TOC levels of the order of 30ppb, conductivity of 1µS and a pH of 7.2 Water were stored in a stainless steel tank and the vent was protected with a 0.2µ hydrophobic filter. It was then fed to the manufacturing areas via a loop. The 47 take off points had zero deadleg volume.
- The water system was routinely sanitized using by circulating water at 80 degree following an SOP.
- The water temperature monitor was located at a point in the loop which was furthest from the storage tank.
- A simulated OQ was conducted manually and compared with computer results
- The PQ involved exhaustive sampling from various usage points at frequent intervals though our year.
- Water was sampled according to SOP.
- 10 ML was tested by the membrane filtration method.
- Warning and action limits were set at 25cfu/ml and 50cfu/ml respectively Chemical and microbiological test results routinely met BP/USP/EP requirements for purified water.

- The record of alarms was inspected, as well as daily monitoring for processing parameters including velocity (flow rate), pressure, temperature, and conductivity. The water loop sanitization was done once a Week.
- Records of preventive maintenance of Carbon Filter.
- Raw water was supplied from a bore well to an epoxy lined concrete tank and dosed with sodium hypochlorite. The water was coarse filtered and softened before treatment with UV irradiation.
- The lamp was guaranteed for 7K hrs but was routinely replaced after 4K hrs. The operating voltage was set at 16K mv. Water was then treated to a second softening stage before RO and EDI treatment.
- Meanwhile PW was transferred to the point of use in stainless steel (SS316) containers. The hold time had been validated up to 72hrs but in reality 2 hrs was the norm. Although the procedure did not contravene any GMP activity, it appeared to be cumbersome in its execution.
- The plan of introducing the water distribution loop was to break through the ceilings and attach Pendants followed by the necessary room requalification.
- The water produced had conductivity prior to EDI of 200µs and 0.43µs post EDI and on standby. In use readings were recorded as 01µs.
- The unit also supplied a storage tank for water to be used for generating pure steam. This tank Was regularly sanitised with recorded F0 values <20
- 3KL SS316L storage tank fitted with a 0.2µ vent filter.
- All gauges and flow meters were tagged with their service Dead legs were minimal (less than 1.5 pipe diameters). Circulation was continuous and the flow rate of 1.2m/sec satisfied the USP requirement, which prevents build up of bio-films.
- The loop was regularly sanitized by circulating the hot water from the steam-heated jacketed holding tank
- Three solutions were used to remove in turn Silica Iron and Bio-film Colloids from RO membranes.
- Deviation forms were attached to Batch Manufacturing Instructions (BMI) and Batch Packaging Instructions (BPI).
- **The following calibration requirements related to the PW system were checked and found satisfactory:**
 - a. Flow meter
 - b. Conduct meter
 - c. TOC meter
- The PW system appeared to be well maintained. PW was produced by RO and associated pre-treatment by softeners and filtration. PW was continuously circulated at ambient temperature which was controlled by a flow meter and temperature.
- Conductivity, flow rate and temperature were controlled on line after the recirculation loop on return to the tank. Flow limit was established NLT 5000l/hour.
- UV lamp working hours and intensity was controlled continuously. Hardness was checked on line before and after softener. Brine solution was used for the regeneration of softener. Regeneration was carried out every two months.
- Back flush was carried out automatically every two hours. The system was sanitized Monthly. Sanitization and maintenance was recorded. Recirculation of the PW was

- Through SS pipe work.
- ▢ Hydrophobic water storage tank filter integrity checks were carried out every month. PW trends for each sampling point were available for inspection, the following tests were performed. All results were within the specifications.
- ▢ Pre-softened water was stored in underground concrete storage tanks, which were regularly cleaned and sanitized with sodium hypochlorite solution.
- ▢ The pipe work of the softening system was made of galvanized iron and thereafter it was in 316L stainless steel. The pipe work welding was electro polished and certified. Photographic evidence was provided. The loop was regularly sanitized by circulating the hot water from the steam-heated jacketed holding tank.
- ▢ The conductivity regularly achieved was of the order of $1.25\mu\text{s}$ and TOC was 60 ± 10 ppb. An outside contractor calibrated the in line TOC meter annually.
- ▢ Water was stored in a stainless steel storage tank fitted with a 0.45μ hydrophobic vent filter. The take off points on the loop were incorporated into ceiling pendants in the work areas. Dead legs were minimal (less than 1.5 pipe diameters).
- ▢ The loop was regularly sanitized by circulating the hot water from the steam-heated jacketed holding tank.
- ▢ Three solutions were used to remove in turn Silica, Iron and Bio-film Colloids from RO membranes.
- ▢ The loop 1 storage tank was examined in order to confirm that a spray ball was indeed used. The absence of dead legs was also confirmed, along with the use of adequate valves (absence of ball valves). Sanitization records were verified for both loops.
- ▢ SOP for Water Sampling.
- ▢ SOP "Equipment Operation of Purified Water Generation, storage and Distribution loop System".
- ▢ Change Control Form, related to the installation of the distribution loop in Building.
- ▢ IQ, OQ and PQ for the re-qualification of the Purified Water Storage Tank and the Distribution Loop System.
- ▢ IQ, OQ and PQ for the re-qualification of the SEPTRON System.
- ▢ IQ, OQ and PQ for the re-qualification of the Ultra-filtration System.
- ▢ Trend Analysis for the quality of Purified Water (covering years wise)
- ▢ SOP for the sampling of water, testing of the water, trends for the qualification of the water system, in accordance with the inspection plan.
- ▢ Hot circulation loop.
- ▢ On line TOC and conductivity monitoring.
- ▢ The clean zone has to be specifically defined.
- ▢ A new water generation, purification and distribution systems had been installed and released to Production after successful stage two of qualification. A change control for the new water purification system and circulation loop had been raised.
- ▢ Various SOPs related to the water system were in place and were reviewed, namely: SOP for regeneration of the softener, RO, water generation, distribution and recirculation System.
- ▢ SOP for the operation of the water purification system.
- ▢ SOP for sanitization of the RO, water generation, and distribution and recirculation system. The Sanitization record was reviewed.

Water purification system Validation:

- The detailed schematic was available in the Site Master File.

(A) Phase One Validation:

- The protocol followed the conventional procedure. URS, DQ, IQ, OQ and PQ were reviewed.
- Validation was carried out, samples were taken daily from all user points for duration of 30 days according with sampling SOP. There were no OOS results obtained during the 1st phase validation.
- PW sanitization SOP was developed after this phase. System was sanitized once per month.
- The water was sampled daily from each take of point for three weeks following an approved SOP.
- The scheduled sample points and the sampling technique ware was adequately described
- A specified sample of raw water was filtered using the Millipore assembly.
- Initial results for raw water were 157cfu/ml (no pathogens) but fell to 85 by the third week.
- This was reportedly due to continuous flushing of the system.
- Initial results for pw were of the order of 40 cfu/ml (pathogens absent, McConkey and selenite growth media) but after three weeks continued sampling the last point in the return loop returned levels between 1 and 12 cfu/ml (USP specification NMT 100 cfu/ml).

(B) Phase Two Validation:

- Samples taken twice weekly for 56 days were tested. Results were similar to phase1.
- Testing was comprehensive in order to accommodate the differing requirements of IP, BP, Ph.Eur and USP.
- The alert limit was set at 50cfu/ml and the action limit at 100cfu/ml.
- Water samples were taken over a period of 30 days. The results were satisfactory.

(C) Phase Three Validation

- Weekly samples again returned result similar to those of the previous validation phases. Trending of raw data showed consistently low levels with no significant spiking.
- Water was regularly sampled throughout the year and covered all take off points.
Water was tested using the membrane filtration method.
- Water Sampling and Analysis Schedule.
- Validation was carried out; samples were taken as per monthly sampling schedule. All Sampling points were sampled on weekly basis. Microbiological and chemical analysis were performed on every sample. There were no OOS results obtained during the 3rd phase validation.

- Qualification, water was regularly sampled throughout the year and covered all take off points. Water was tested using the membrane filtration method. Raw data seen during the microbiology laboratory audit showed levels of the order of between 3 and 5cfu/ml absence of pathogens. Computer generated trend charts showed a level performance with an alert limit set at 60cfu/ml. This is well below the USP maximum of 100cfu/ml. It was suggested that the alert limit could be lowered to a level more representative of the actual levels being found.

Design Qualification and User Requirement:

- URS were generated by the QA manager and the OQ specified the performance and operating characteristics. All parts were named including the water softening equipment.

Installation Qualification:

- This was undertaken by the unit's manufacturer and monitored by Maintenance engineering manager of the company where installation took place.
- The pipe work internal weld surfaces were certified as electro polished. All equipment had been calibrated as exemplified by the flow meter, pressure gauges on/off switch sensors and the conductivity meter.

Operational Qualification:

- The system was sanitised prior to OQ. All modules were checked for correct working. The Relevant SOP had been finalized but was yet to be authorized.
- Assessment included the two major circulation pumps, and the RO cartridge material.
- Operational Qualification. Random selection of data for valves controlling flow rate were assessed together with the actual flow calculations.

Performance Qualification:

- PQ was satisfactory as demonstrated by chemical and microbiological test results. The water sampling procedure, microbiological tests and validation of the recovery and detection of the low levels of micro organisms anticipated, all followed approved SOPs.
- Samples could be kept for up to 2hrs before chemical testing and up to 8 hrs at 0 Deg C for microbiology
- The water was sampled daily from each take off point for three weeks.
- Sampling followed an SOP which described the scheduled sampling points and the sampling technique.
- A specified sample of raw water was filtered using the Millipore assembly.
- Qualification: Water samples were taken over a period of 30 days.

- Full documentation of media and growth promotion testing was recorded. For 28 consecutive days, samples from the sampling port and the flexible hosepipe used for filling the stainless steel vessel used in transport were tested.
- pH values were repeatedly 5.7 (spec 5.0 to 7.0), TOC 48ppb (spec 500ppb), raw data for bio-burden was between zero cfu/ml and 8cfu/ml. Pathogens were not detected. It was noted that the absence of fungi was not recorded. It was accepted that the company had yet to find any

Engineering services and utilities features included:

- UPS
- Air compressors
- Boiler
- Chiller
- AHUs Planned Preventive Maintenance
- Calibration
- Installation
- HVAC validation