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Managing Project of Water Purification System

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Abstract: Purified water is the minimum quality of water used in compounding medicines. Pharmacopoeias define the specifications of purified water. Drinking water is the required feed water to the purification system which should be subjected to pretreatment process to remove water hardness and particulate. Treatment system may require different technologies and should be designed to remove impurities and control the chemical and microbiological contamination. Regulatory authorities define cGMP for design, material of construction to be used and installation control parameters as well as control systems for operation. USP defines three stages for validation which consider consistent and extended production with alert level and action level. Particulate, conductivity, total organic carbon and microbial count are the key parameters for efficiency of the system. Risk analysis requires defining of critical control points and attributes to be assessed.

Key words: water purification systems, user requirement specifications for water treatment system, validation of purified water production, risk analysis of water purification system.

I. INTRODUCTION

BP 2016[1] defines purified water as the water for the preparation of medicines other than those that are required to be both sterile and apyrogenic, unless otherwise justified and authorized. Purified water in bulk is prepared by distillation, by ion-exchange, by reverse osmosis or by any other suitable method from water that complies with the regulations on water intended for human consumption laid down by competent authority. Purified water in bulk is stored and distributed in conditions designed to prevent growth of microorganism and to avoid any other contamination. Treatment may be used first to achieve drinking-water quality and subsequently purified water. PW must not contain any added substances.

1.1 Specifications of Purified water USP[2]:

Conductivity: Stage 1 Temperature – conductivity table specifies 1.3µ*S*/cm at 25 ºC. Stage 2 depends on the absorbability of CO_2 and stage3 is pH dependent.

Total Organic Carbon : TOC analyzer oxidize organic molecules into CO_2 which could be determined. The analyzer should have detection limit of 0.05 mg carbon per litre or lower. USP reference standard is 1,4-benzoquinone RS, Sucrose RS. 0.5 mg/litre is the USP limit.

Microbial: Under normal conditions, 100 cfu/ml determined by filtration through 0.45 um, using R_2 Agar and incubated at 30 – 35 ºC for 5 days, is an appropriate action level.

1.2 Specifications for drinking water: *WHO good manufacturing practices: water for pharmaceutical use – WHO technical report series No. 970, 2012 PP 67- 89*

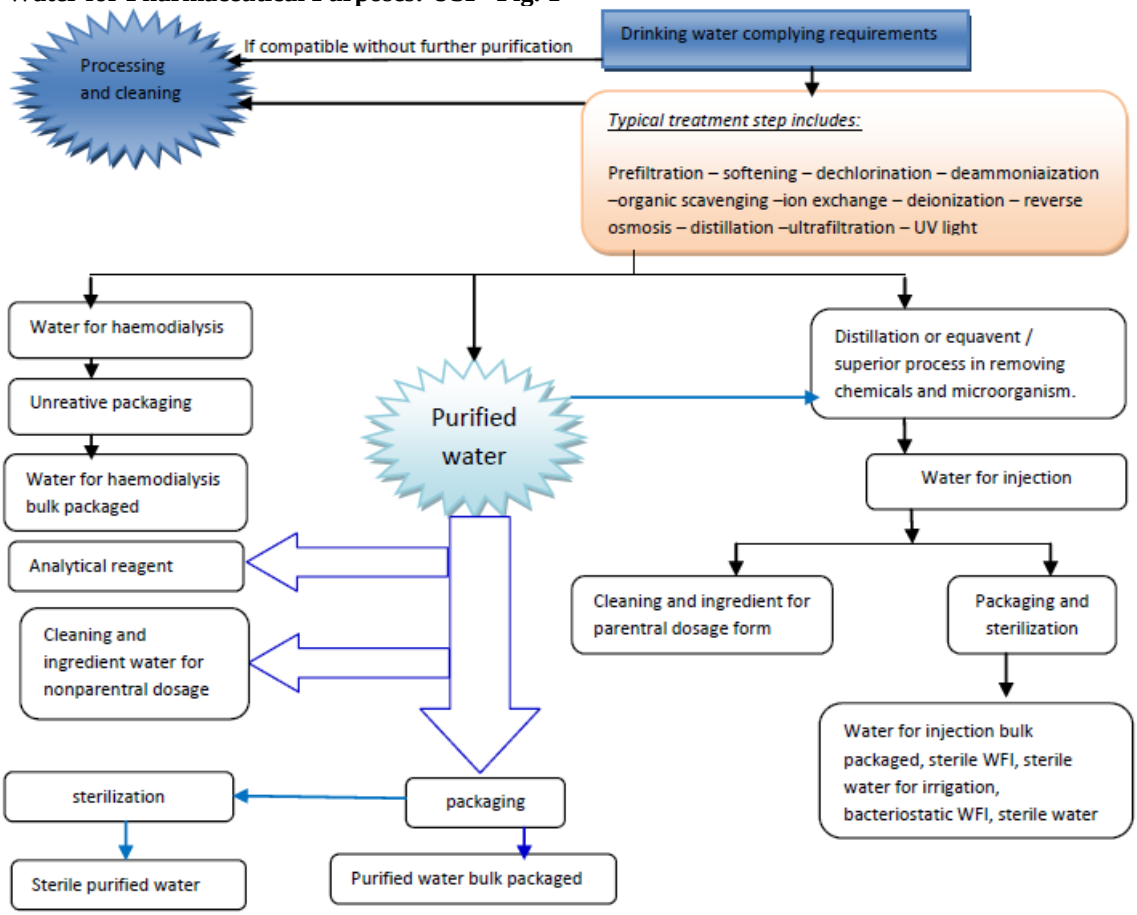
Typical treatment includes desalinization, softening, removal of specific ions, particle reduction and microbiological treatment.

3.2.5 It is the responsibility of the manufacturer to assure that the source water supplying the water treatment system meets the drinking water specifications. There may be situations where water treatment is used first to achieve drinking-water quality and subsequently purified water. In this case the point at which drinking-water achieved should be identified and tested.

1.3Water purification technologies:

Alum treatment, Chlorinated or bleaching powder, Activated carbon filter, Sand filter or quartz filter, Ion-exchange water softening, Ion-exchange deionization, UV light, Ozonization, Distillation, Membrane filtration including, microfiltration, ultrafiltration, nanoflitration, electro dialysis reversal, electro deionization and reverse osmosis.

1.2 Water for Pharmaceutical Purposes: USP[2] Fig. 1



II. DESIGNING

Defining capacity as quantity per time and diversity demand and future expectation, recirculation to be chemically and microbiologically controlled, specifications of water should be adequate to process and product and consistent in quality. The performance indicators should be monitored and the process should be validated.

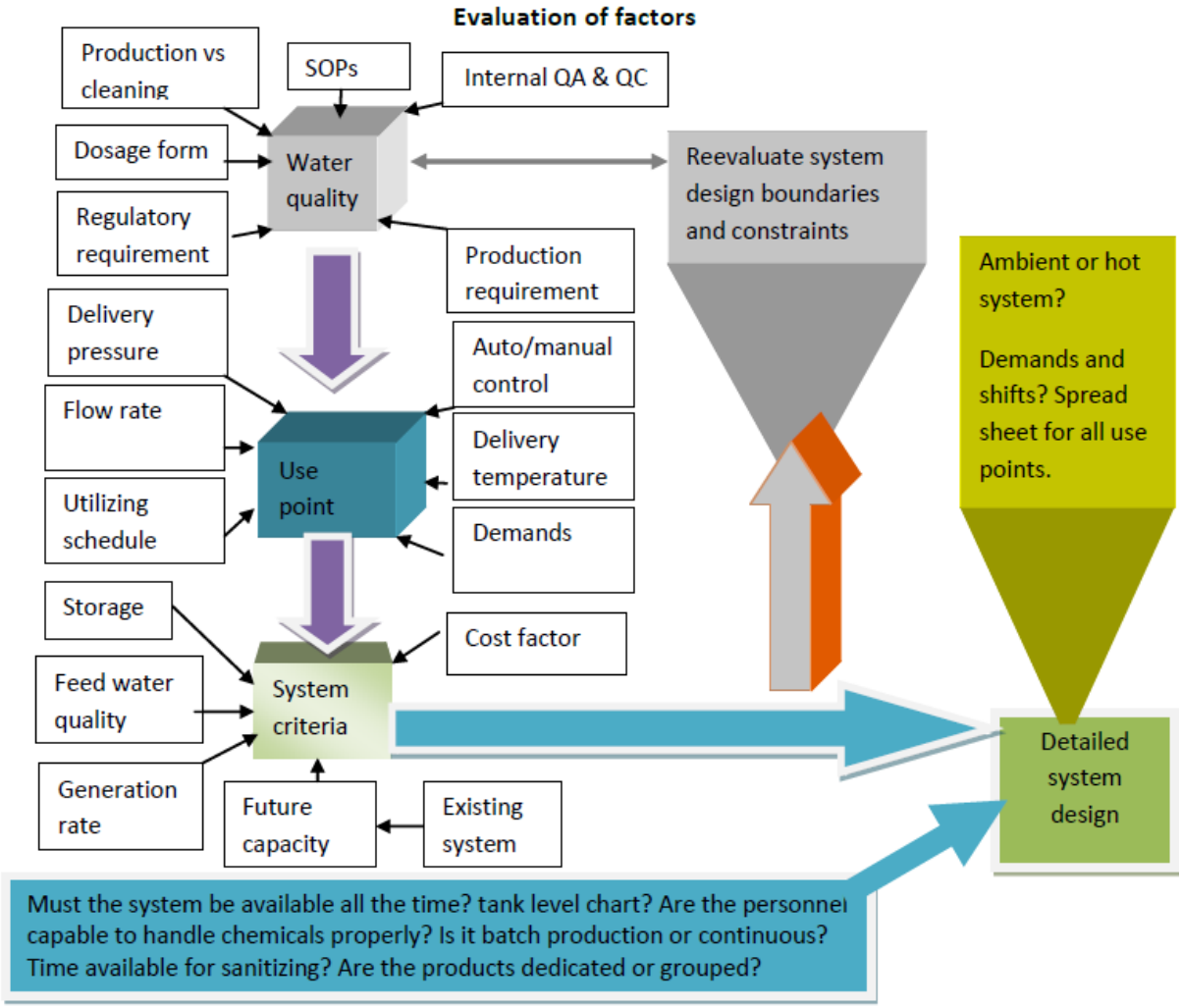
2.1 Water options and system planning

1. The capacity of the system should be designed to meet the average and peak flow demand of current operations, further demands, increase in capacity and modification.
2. Appropriate recirculation to be chemically and microbiologically controlled.

- Water quality should be determined based on the final product, specifications of water should be adequate to process and product.
- Water should be produced consistent in composition and quality and the key performance indicators should be monitored and the process should be validated.

2.2 Factors to be considered:

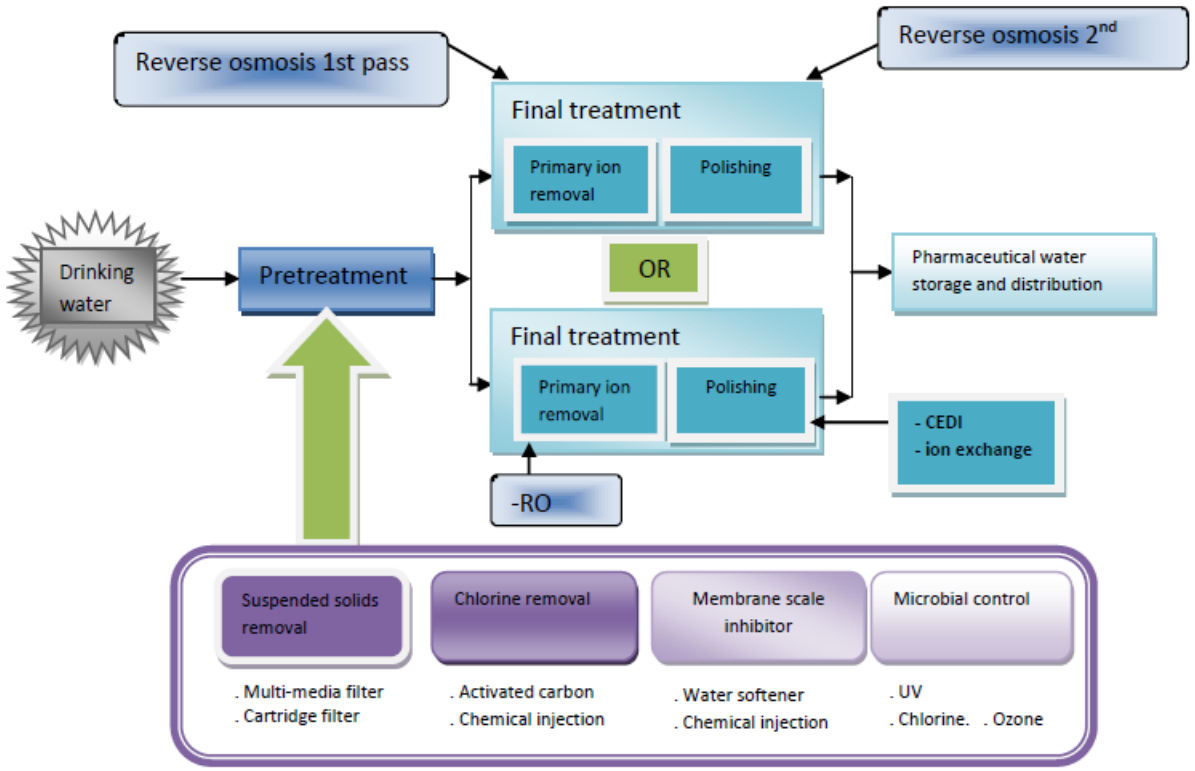
The FDA[3] guideline 1993 considers that although the use of heat could turn out to be expensive than other system, it does lower control and maintenance costs and reduces potential problems in the production system for purified water.



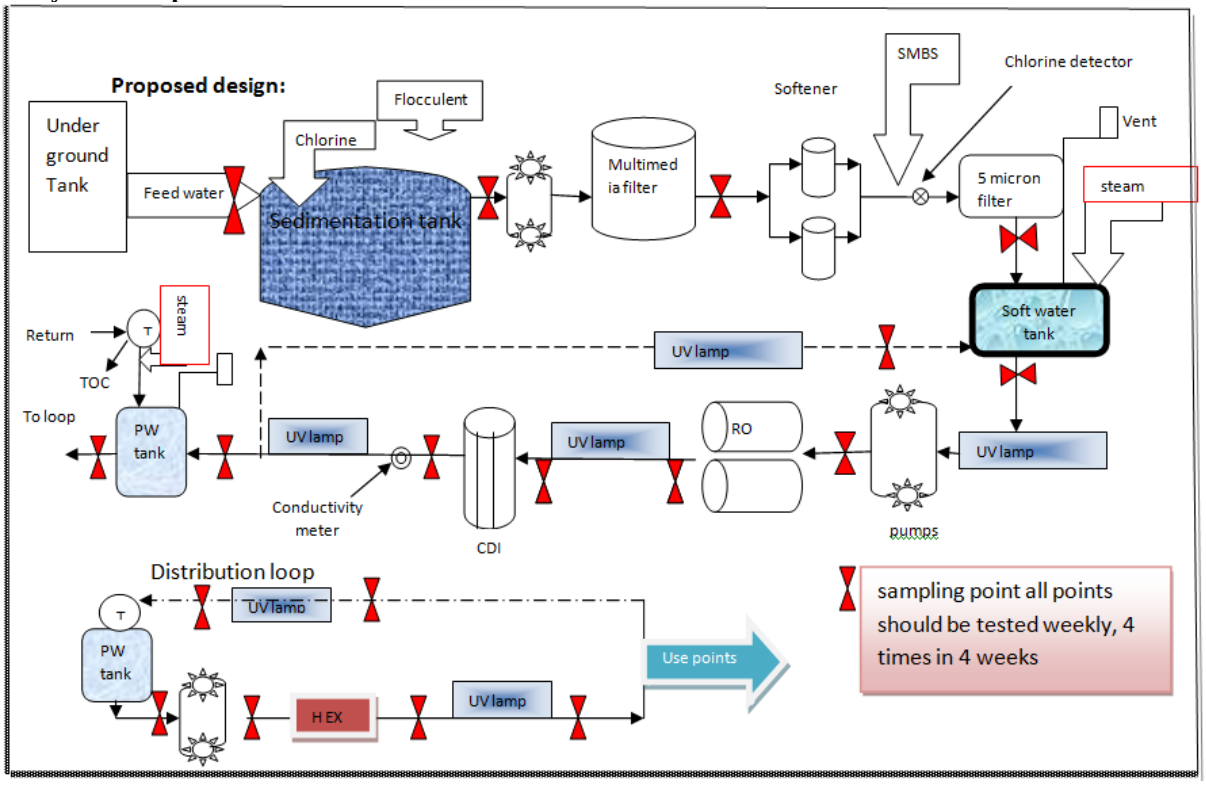
2.3 Removal of impurities[8]:

Impurities	Microbial	Undissolved	Dissolved
Way of Removal	Disinfectant dosing Sod.HCl_3	Sand/ quartz filter	
	UV radiation	10,5,1 micron filter	
	UF / Sterile membrane filter	Coagulant dosing alum	Polymer dosing
	Ozone		RO
	Hot water recirculation		DI
	Maintaining velocity flow.		EDI
	Vent filters to storage tank		Distillation
	Distillation		UF / Nano

2.4 PROCESS DESCRIPTION AND FLOW DESIGN[5]

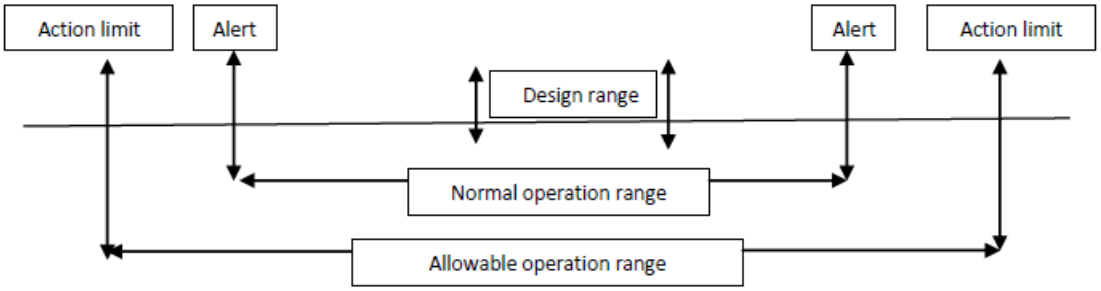


2.5 System components:



2.6 Design range and operating range[5]

- Design range: the specified range or accuracy of a controlled variable used by the designer as a basis to determine the performance requirements for an engineered water system.
- Allowable operation range: the range of validated critical parameter within which acceptable product water can be manufactured.
- Normal operating range: a range which may be selected by the manufacturer as a desired acceptable value for parameter during normal operations e.g conductivity. This range must be within the allowable range.
- From cGMP point of view the system should operate within allowable operation range.



III. SOURCING AND PROCUREMENT

3.1 General:[6] In the procurement process the vendor is required to make demonstration for procedures of operation, validation and regulatory compliance. Sourcing Team should identify reliable vendor capable of providing high quality products to meet the schedules considering cost of material, cost of time and soft cost.

3.2 Selection criteria[7]**:**

Criteria are the price, ability to meet specifications and standards, product service quality and durability, reliable delivery method, quality control methods and practices, technical ability, financial stability, adequate distribution history, spare parts availability, warrantee, insurance and bonding provisions, performance and experience as well as after sale service, training and time table commitment. Supplier should be strategic.

3.3 Criteria of evaluation[7]**:**

a) Process –based evaluation: assessment based on production or service process.
b) Performance – based evaluation: an audit conducted to supplier site to assess the level of capability in his system.
c) Additional criteria: ISO – 9001 -2008 certification or Maclcom Baldrige National Quality Award or any other related internal certificate.
d) General evaluation: categorical method, cost-ratio method and linear-average method.

- Categorical method: categorizing each supplier performance in a specific area defined by a list of relevant variable. Performance factors, grades are good, neutral and satisfied.
- Cost – ratio method: cost analysis = selling price + buyer internal operational cost + quality attributes + delivery lead time + service elements.
- Hidden cost evaluation: product life time.

Attribute	**Quality**	**Delivery**	**Technology**	**Price**	**Service**	**Total**
Score	30	25	20	15	10	100

If the score is 80: (100 -80)/100 + 1 = 1.2 that means for every I dollar there is 20 cent added from this line downtime.

IV. USER REQUIREMENT SPECIFICATIONS

4.1 Quality:

4.1.1 Feed Water to PW System is potable water the quality of which is summarized below:

Physico-chemical and chemical tests * Minimal and maximal in period January to December			
Parameter	***Unit***	***Acceptance criteria***	***Results****
Odour	-	*Odourless*	*Odourless*
Colour	*°Co-Pt scale*	*< 5*	*No colour*
Turbidity	*NTU units*	*< 1*	*1.1 – 13*
pH	-	*6.8 – 8.5*	*7.5 – 8.5*

Conductivity 20 °C	*µS/cm*	*< 1000*	*199 – 357*
Residual chlorine	*mg/l*	*< 0.5*	*NA*
Chlorides	*mg/l*	*< 200*	*7 – 18*
Ammonia	*mg/l*	*< 0.1*	*0.05 – 0.19*
Nitrites	*mg/l*	*< 0 .03*	*0.003 – 0.32*
Nitrates	*mg/l*	*< 50*	*1.7 – 4.5*
Iron total	*mg/l*	*< 0.3*	*0.01 – 0.08*
Manganese	*mg/l*	*<0.05*	*0.001 – 0.031*
Microbiological Tests			
Total aerobic mesofile bacteria count per 1 ml		*< 10*	*NA*
Total coliform bacteria in 100 ml		*0*	*NA*
Absence of		*Pseudomonas aeruginosa, - Burkholderia cepacia - Enterobacteriaceae*	*Absence*

4.1.2 REQUIRED PW QUALITY[2,9]

PW shall comply with the current versions of the specifications required by both European Pharmacopoeia and the USP, at all of the user points.

Parameter	***Unit***	***Specification***	***Reference***
Appearance		*Clear liquid*	*Ph.Eur.*
Colour		*Colorless*	*Ph.Eur.*
Odour		*Without*	*Ph.Eur.*
Conductivity	*µS/cm*	*≤ 1.3 at 25°C*	*USP*
TOC	*ppm*	*≤ 0.5*	*USP, Ph.Eur.*
Additives		*No added substances*	*USP*
Heavy metals	*ppm*	*≤ 0.1*	*Ph.Eur*
Nitrates	*ppm*	*≤ 0.2*	*Ph.Eur*
Microbiological Specifications (TVC)			
Alert limit	*Action limit*		*Reference*
50 cfu/ml (5000 cfu/ 100 ml)	*100 cfu / ml (10,000 cfu/ 100 ml)*		*USP, Ph.Eur*
Absence	*Pseudomonas aeruginosa, - Burkholderia cepacia - Enterobacteriaceae*		

4.2 cGMP Compliance[8]

European GMP A1-31 water treatment plant should be designed, constructed and maintained so as to ensure the reliable production of water of an appropriate quality. They should be operated within their designed capacities. Water should be produced, stored and distributed in a manner which prevents microbial growth, for example by constant circulation in a temperature over 70 °C.

- Quality of installation, sampling and testing procedures, operation and maintenance procedures should be documented.
- Continuous turbulent flow Renyolds above 2000.
- Elevated or reduced temperatures. Circulation 65 – 80 °C.
- Smooth clean surfaces, electro polished 280 grit.
- Frequent draining flushing and sanitization.
- Positive distribution loop pressure.
- Properly DQ,IQ, OQ, PQ and maintenance.
- No dead legs. Slope verification test of piping.
- Vent filter integrity.
- Verify water quality after each step of purification.

4.3 PURIFICATION[8]

4.3.1 Feed water:

Polypropylene tank equipped with service pump with high and low level probes in the treated water tank to switch on and off for the pump. The tank equipped with low level probe to activate feed water pump from the source.

4.3.2 Pretreatment system:

Water pumped from the tank with a uniform flow rate being regulated by valve and flow meter.

Chlorine is dosed for disinfection and removed later, alum polymer to settle smaller suspended undissolved impurities in the settling tank where it aggregates. Water is pumped into multimedia filter to trap aggregates. Antisaclant dosing can help in removal of dissolved reactive silica. Sodium metabisulfite is dosed to neutralize chlorine and removal is controlled by Oxidation-Reduction Potential Meter and dumping valves. If water chlorine is above the limit, it goes to drain.

4.3.2.1 Multimedia:

Multimedia consists of gravel, manganese green sand and anthracite. The purpose is to remove solid particles down to 7 – 10 µm from the incoming source water and protect downstream system components. It is suited near the head of the water pretreatment system prior to unit operations designed to remove water disinfectants. Back wash using feed water (time controlled).

4.3.2.2 Organic scavengers: These are macro reticular weakly basic anion-exchange resins. They remove organic materials and endotoxin from water. To be regenerated by caustic brine solutions.

4.3.2.3 Carbon Filter: Use chemviron Filtrasorb 200 withgravel under fillto remove residual chlorine and some organics. The bed size is EBCT value of 2 -5 for free chlorine and 7.5 -12 for chloramines. To be sanitized by hot water or steam, UV in the inlet and fines must be drained.

4.3.2.4 Softener: Water softener unit may be located upstream or downstream of the disinfection unit. They utilize sodium based cation-exchange resins (Sodium Zeolite) to remove water hardness ions (calcium and magnesium). They can also be designed to remove ammonium ion and located downstream to disinfection to remove liberated ammonia from chloramines. In this case, pH, contact time, resin surface fouling and regeneration frequency are important. Regeneration use brine solution.

4.3.2.5 Materials of construction[8]:

Pipes: if not using heat, plastic PVC,CPVC, PPR could be used. Copper or galvanized steel.

Vessels may be fiberglass, lined carbon steel or stainless steel.

Valves are Ball or diaphragm and needle valve for flow control.

4.3.2.6 Out- put water quality from the pretreatment process:

Silt of 3-5 SDI and Hardness < 1 grain/gallon.

4.3.3 Treatment[5]:

Reverse Osmosis followed by Continuous Electro Deionization and Polishing. Purification System shall allow recirculation when PW is not being fed forward. Purification system is to be capable of thermal sanitization. Membrane degassing system is to be provided prior to the RO membrane, UV lamp is to be installed for neutralization of chlorine and reduction of the microbial content of the incoming water. This unit will have higher radiation on 185nm wave length. For monitoring of chlorine neutralization effectiveness, chlorine analyzer is to be installed. Mechanical filters are to be installed prior to the RO membranes for the reduction of particles and protection.

4.3.3.1 Reverse Osmosis:

Permeate 75% and rejects 75% of which 80% to be recirculated.

- ✓ Significantly reduce chemical handling and disposal.
- ✓ Integrity testing can be accomplished by salt challenges and measurement of conductivity.
- ✓ Remove a wide range of contaminants including ionized and no ionic, bacterial endotoxin and some dissolved organics.

4.3.3.1.1 Membrane: Polyamide Thin Film Composite working conditions

pH	2 -11	Sanitization temperature limit	50 – 80 ºC
Chlorine limit mg/L	0.05	TDS feed range mg/L	30 – 1000
Operation temperature range	5 – 50 ºC	Silt density index, max	5
Rejection %	97 – 99 %	Resistance to bacteria	Good

4.3.3.1.2 Permeate recovery rate:

Higher pressure increases the recovery rate and decreases the purity of permeate. When increased pressure yields the same permeate this indicates the blockage of the membrane. The permeate purity can be achieved by a second pass of the membrane through another RO stage. Flushing membrane with permeate upon shutdown, allows the membrane to reside in a non- fouling state.

4.3.3.2 Continuous Electrodeionization CEDI:

After pretreatment and RO, it permeates 90% and rejcts 10%. Temperature limit 10 – 40 ºC. To remove ionized solids reduction more than 99%, produce 1 – 18 Mohm-cm water resistivity from RO feed water. Organic rejection 50 – 95 %, removes bicarbonate of dissolved CO_2. Materials are PVC or stainless steel. EDI provides water of conductivity at 25 ºC lower than USP 1.3 uS/cm. CEDI systems are combination of mixed resin, selectively permeable membrane and electric charge. It provides continuous flow of product water and waste

concentrate and continuous regeneration. The electrical potential also separates water into H^+ and OH^- providing continuous regeneration of the resin. CEDI unit cannot tolerate heavier ion load. Control measures includes re-circulating loop and effluent microbial control by UV, conductivity monitoring, resin testing, micro porous filtration for mixing air, microbial monitoring by frequent regeneration, monitoring of the rechargeable canisters.

4.3.4 Polishing

4.3.4.1 Ultrafiltration:

For purified water with low endotoxin < 0.25 EU/ml. (ophthalmic and topical). UF is used to feed still water to limit endotoxin and colloidal silica. It provides 2-4 log endotoxin reduction. Ultra filtration membrane made of polyethersulphone; they are hygienic and have thermal tolerance. So, used at the point of use to remove bacteria and endotoxin. Ceramic ultrafilters are most durable being self-supporting, backwashable, chemically cleanable and steam sterilizable but it needs higher operating pressure. Ultrafilters with molecular weight cutoff rating 10,000 to 20,000 Da are typically used in the water systems to remove endotoxins. Waste can be recycled to RO or cooling tower or others.

4.3.4.2 Microfiltration:

Membrane filter is pore size 0.45 µm to 0.04 µm. Microbial Retentive Filtration to retain negatively charged endotoxins. 0.2 -0.22 um, 0.1 um was preferable and more tight. It should be Hydrophobic.

4.3.4.3 UV light: 254 nm design for microbial reduction and 185 nm for TOC reduction. Control measures includes regular inspection to detect bulb failure and occlusion film, regular bulb cleaning and wiping and yearly replacement and use of chlorine detector downstream. Particulate can shield from UV.

4.4 Storage system: Systems should be designed to be fully integrated with the system components and to prevent microbial proliferation and recontamination. The system should be subjected to online and offline monitoring. Configuration should allow for continuous flow of water in piping by recirculation without dead leg.

4.4.1 Storage tank[10]:

4.4.1.1 Design: Tank can be vertical, cylindrical- dished end to allow complete drainage. Design pressure: -1/+3 bar; Pressure probe for vapour pressure during sanitization; and alarm bursting disc**.**

Wetted surfaces AISI 316L; pickled and passivated, Ra < 0,8 µm. Connections: Manholes, water inlet, water outlet, loop return. Shell and bottom are insulated with min. 40mm thick glass wool layer, protected with cladding from AISI 304. Spray ball on the top. Heat jacketed, drainable, hydrophobic vent filter, 0.2 µm,; Temperature probe, sampling port and Level indication, Low level sensor opens the solenoid valve to let water flow into the tank and if the level is too low, it switches off the distribution pump. High level sensor closes the solenoid valve. Nozzles should avoid dead zones.

4.4.1.2 Capacity:

The water treatment equipment should be able to operate continuously for period to avoid on/off stress. Tank returnover 1 – 5 times per hour. Should provide reserve capacity equal to water to complete process batch + work session + tank turnover by circulation + logical period of demand.

4.5 DISTRIBUTION SYSTEMS

4.5.1 Design requirements:

Distribution System shall ensure turbulent flow with nominal velocity of 1 – 3 m/s. Minimal pressure of 4 bar in return loop is to be provided. It shall incorporate hydraulic balancing features to enable normal operating conditions are satisfied without loss of pressure as points of use are opened.

4.5.2 Requirements for distribution pumps

Sanitary centrifugal design, constructed from AISI 316L; capable of being drained; double sealed and capable of high temperature sanitization (max 95°C), surface finishing: Ra < 0,8 µm; sampling points before and after the pump. Delivery line of pump shall be provided with flow meter then 5 micron filter then UV.

4.5.3 Piping

The target is to have fully welded system. The design of the route of PW distribution piping shall aim to minimize the number of welds and bends throughout the system. Where equipment or instrumentation is connected to the piping system tri-clamp shall be used. The piping will be auto-drainable, with a slope of 1% up to the next drainage point. Dead legs in all effluent piping will be limited to 3D. Sampling valves are to be provided at each point of use and after each component.

4.5.4 Material of construction[5]

Stainless steel can provide corrosion resistant, microbial activity resistant and chemical sanitizability. Auxiliary equipment and fittings; gaskets, seal, diaphragms, filter media and membranes should exclude possibility of extractables, shedding and microbial activity. Insulation material exposed to stainless steel surface should be free of chloride. Heat exchangers should be constructed to prevent leakage of heat transfer medium to

water and there should be a mean to detect leakage. Valves should have smooth internal surfaces with the seat and closing device exposed to the flushing action of water such like that of diaphragm valves.
Acceptable plastics are poly propylene, polyvinylidene – diflouride and perflouoroalkoxy.
4.5.6 Surface finishes: Sheet steel,pipes and fittings internal surfaces - Ra ≤ 0.8 μm and external surfaces- Ra ≤ 1.2 μm, Non-product contact parts in pharmaceutical zone: all surfaces - Ra ≤ 1.2 μm.

CONTROL SYSTEMS[5]
PW System is to be fully automated for normal operation and periodical sanitization in conformity with GAMP 5. Electronic data recording system is required. Controlling and monitoring the proper operation of the whole PW System, including all system components: feeding water pre-treatment, purification system, storage tank and distribution loop, is to be provided via one Control Panel.
The following controls and recordings are required flow meter – Corriolis type), loop return conductivity, TOC analyzer, temperature in the distribution tank and loop/heat exchanger, pressure gauges. Indication of PW usage somewhere in the system is to be provided. All sensors are to be calibrated and certified and capable of being sanitized at 90° C. Deviations from set values shall lead to an audible and visible alarm. UV lamp should be provided with intensity indicator.

4.7 INSTALLATION and COMMISSIONING

4.7.1 WELDING
A qualified welding installer experienced with thin wall orbital welding for pharmaceutical industry. The installer will be required to submit written weld procedures. Stainless steel welding under Argon arc and treated by pickling and passivation. All welds shall be crack and crevice free. Internal welds shall be ground smooth and flush. Welds shall be polished, shall be made with automatic orbital welding equipment and numbered and certified. Traceable documentation, including printouts from the machine, giving daily parameters, is required.
Internal visual inspections with a video probe of all manual and 20% of orbital welds shall be taken.
The pipe work system is to be cleaned and passivated after welding 'As-built' documentation must be done. No threaded connections.

4.7.2 EQUIPMENT IDENTIFICATION
On each equipment and component including all sampling and take off points, a washable and nonremovable label mentioning the tag number will be attached. Flow direction has to be identified.

4.7.3 FACTORY ACCEPTANCE TESTS (FATS)
Factory Acceptance Tests shall be conducted at the premises of the Vendor in accordance with written procedures and protocols. Tests must ensure that the equipment conforms to the design requirements and its compliance with the specification
The approval of the Factory Acceptance Tests shall not constitute acceptance of the machine.

4.7.4 Site acceptance tests (SATS)
The equipment is to be installed in the proposed location. All the design information to ensure proper civil works as well as details of floor/foundation and loading, personnel with special tools, measuring devices, drawings and data necessary for performing their duties should provided.
Point to point checks on wiring and pneumatic should be performed. **I**nstruments should be properly calibrated. The commissioning should demonstrate that the equipment supplied has been properly installed and that the functions are in accordance with the specification, manuals and other documents. It shall demonstrate that the system will operate as intended throughout all anticipated operating ranges. It should consider description of item and its function, reference manuals required to carry out a test, equipment used, and date of calibration, methods, and acceptance criteria, results and conclusion.

4.8 Training: Training of operating and maintenance staff in the relevant procedures should be conducted at the manufacturer site and at the client site. Training will be required in set up, commissioning, control adjustment, maintenance, sanitization, trouble shooting, cleaning, dismantling and re-assembly.

V. VALIDATION AND QUALIFICATION

Validation is the process when by substantiation to a high level of assurance that a specific process will consistently produce a product conforming to established set of quality attributes is acquired and documented.

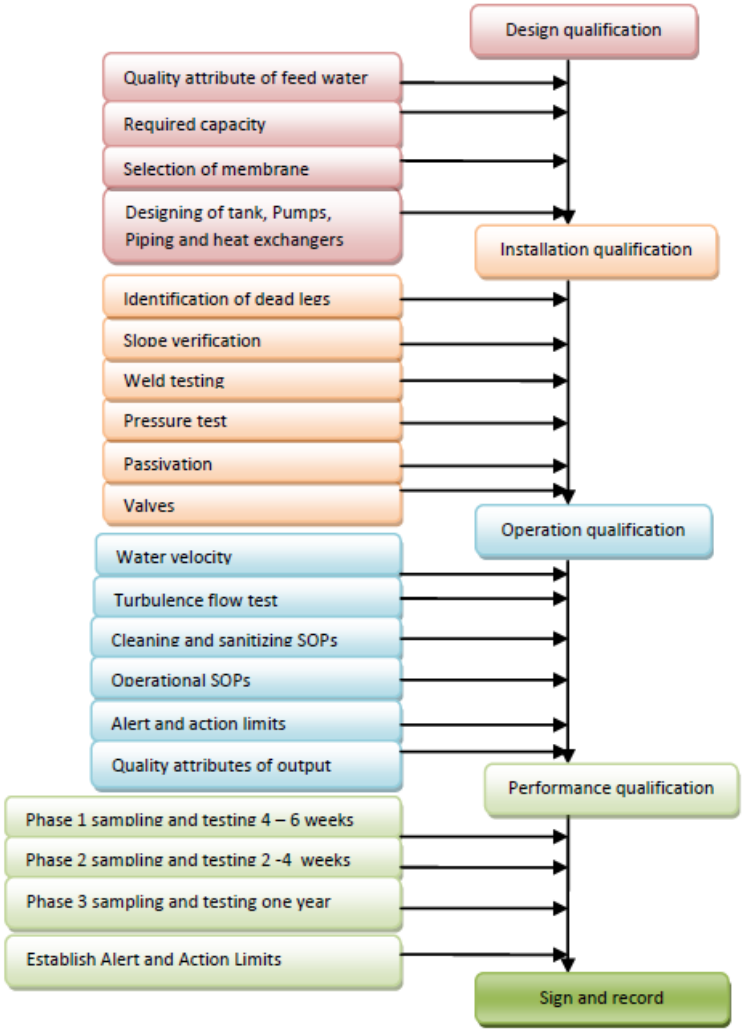
5.1 Validation Plan[3]:

1. Establishing the standards of the quality attributes of the finished water and the source water.
2. Defining the unit operation and their operating parameters.
3. Developing an IQ stage to verify that the installation meets the design requirements.
4. OQ stage consisting of tests and inspections to verify that the equipment, the system alerts and controls are operating reliably and the action levels are established.
5. Developing prospective PQ stage to confirm the appropriateness of the critical process parameter operating range for the key quality attributes and operating parameters are verified.

6. Assuring the adequacy of the ongoing control procedures.
7. Changes control, preventive maintenance and recalibration of instruments.
8. Schedule for periodic review of the system performance and requalification.
9. Completing protocol and documenting steps from 1 to 9.

5.2 System Validation: It would be undesirable to introduce microorganism into an on-line system. Validation should include heat distribution. Validation report should describe the system with a print and drawing. USP[2] defines phase 1, phase 2 and phase 3 for system validation.

5.3 Stages of water system qualification[11]:



Phase 1: Daily testing of source water for two weeks, the system should work continuously without deviation. The tests include:

1. Chemical and microbiological tests according to a according to the SOPs to be developed.
2. Sample and monitor after each purification step.
3. Sample and monitor at each point of use.
4. Develop appropriate operation range.
5. Develop and finalize operating, cleaning, sanitizing and maintenance procedures.
6. Demonstrate production and delivery of product water of required quality and quantity.
7. Use and refine SOPs for operation, sanitizing, maintenance and trouble shooting.
8. Verify provisional alert levels.
9. Develop and refine test-failure procedure.

11.4.2 phase 2: Carried out for 15 days after successful phase 1.

- Sample scheme same as phase 1.
- Carryout monitoring deploying all the refines SOPs.
- Demonstrate consistent operation within established range.

- Demonstrate consistent production and delivery of water of the required quality and quantity when the system using the SOPs.
- Water can be used for manufacturing during this phase.

11.4.3 Phase 3: Data obtained should demonstrate that when the system is operated in accordance with the SOPs over a long period of time it will consistently produce water of the desired quality considering the seasonal variations. Sampling shall be as routine for one year.

The last part of validation is compiling the data and conclusion, signed and approved.Typical successful SOPs should consider the contamination of water by non-sterile air remaining in the pipe after drainage. The major consideration is the acceptance criteria throughout the system.

FDA considered one way system as a dead leg and generally not acceptable but for 50 points of use in 200 yards long of system, using good SOPs, validated base, routine hot flushing water 80 ºC, the system seems to be acceptable. Ozone has hazards to the system and employee safety.

VI. OPERATION

Check the SDI, adjust pH by NaOH to 8 for RO then filter by 5 micron, then pass through RO. Repeat RO till having conductivity below 30 -40 uS/cm, Co2 less than 1ppm, hardness less than 100ppm.

With water pressure 2kg/cm2, pass water through 0.45 micron filter, collect 500 ml in time T1, then after 15 minutes T2. SDI = (T1 – T2)/ (T2×15) ×100 it should be below 4.

6.1 A routine monitoring plan:

Online instruments with qualified alarm systems of parameters and offline chemical and microbiological testing. Frequent sampling from use points. Preventive maintenance. Control of changes in the mechanical system or conditions.Trend analysis towards frequently exceeding alert limit should trigger an investigation and corrective action.

6.2 Sanitization:

6.2.1 Thermal periodic, circulating water 80 ºC and steam or continuous; circulating water at 65 ºC.

6.2.2 Chemical Complete removal of the sanitant from the system and detection of its residues is essential. Frequency of sanitization should be determined by the result of microbial monitoring.

1. Ozone could be used continuously and effectively because it degrades into oxygen by UV.
1. Citric acid to remove inorganic foulants, Sodium hydroxide removes organic foulants.
2. Formaldehyde / H2O2/ peracetic acid. Consult the manufacturer for concentrations

Chlorine of 0.3 -0.5 mg/L tested by diethylphenylene diamine kit.

6.3 Microbial control

6.3.1 **General** During sanitization, temperature and exposure time should be considered. Turbulent flow. Water velocity test at each point should not be less than 1.5 m/sec. Reynolds number measures the turbulence of water flowing in the distribution pipelines should be above 2000 to remove the biofilm 5 ft/sec + ozone or chlorine over long period. Shorter possible length of pipework. Dead legs should be minimized or avoided not exceeding 3 times the ID pipe measured from the centre line of the use point. Pressure gauges should be separated from the system by membranes. Hygienic pattern diaphragm valves should be used.

6.3.2 Alert Level and Action Level[12]:

USP: Total microbial levels and objectionable organism should always be below water specifications.

- Maximum 100 cfu/ml for purified water. sample size minimum 1 ml for USP and 100 ml for FDA.
- Action limit Drinking water is 500 cfu/ml.

WHO[12] bacterial limit cfu/ml, sampling procedure, integrity, size and training are prerequisites

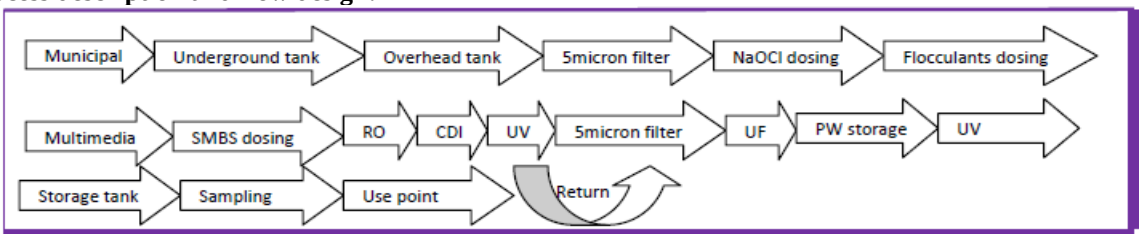
location	Target	Alert	Action	location	Target	Alert	Action
Raw water	200	300	500	Post carbon filter	50	300	500
Post multimedia	100	300	500	Feed to RO	20	200	500
Post softener	100	300	500	RO permeate	10	50	100
Point of use	1	10	100				

6.4 Maintenance: The conductivity and TOC can quantitatively assess the water chemical purity as a function of routine maintenance and regeneration scheme. The extent and type of maintenance must be in accordance with Good Engineering Practice and Equipment Manufacturers directions.

6.5 Risk analysis and risk management[8]

Hazard analysis as per HACCP guide to identify hazards and recommend controls, critical limits, and corrective action and verify the effectiveness of procedures.

Process description and flow design:



List of hazards

	Process step	Hazard	Biological	Chemical	Physical	Adverse health effect

Evaluation of probability and severity and control measures:

	Potential hazard biological, chemical and physical	**Severity of potential hazard**	**Probability of occurrence**	**Existing control measures**	**New control measures**

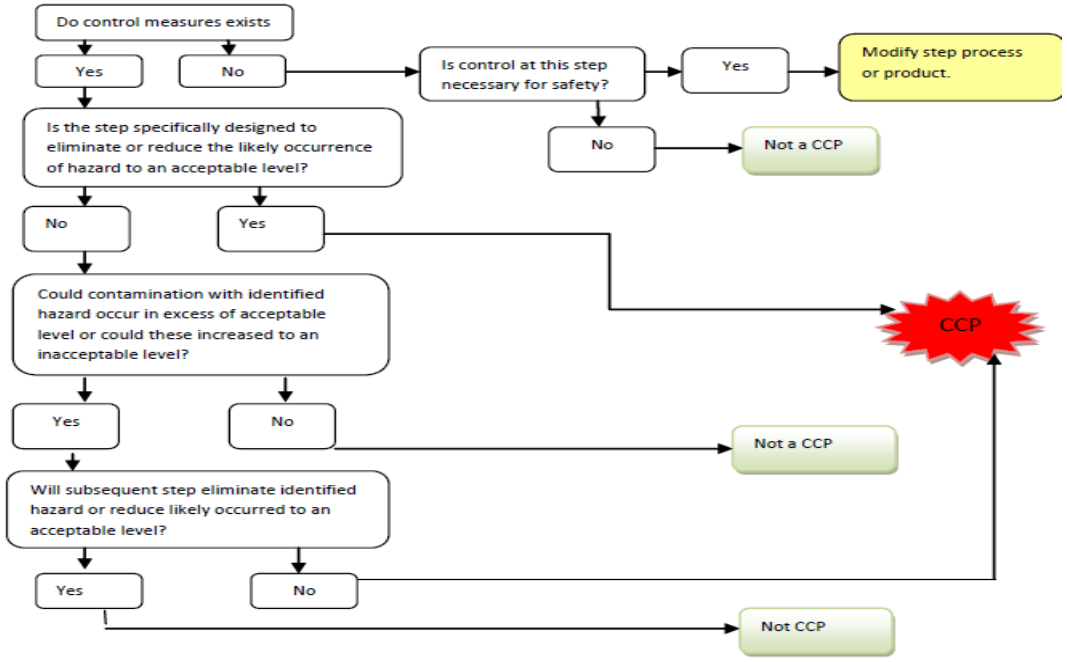
Potential Critical Control Points PCCP:

		Water supply	softener	Storage	Process
Parameter	Unit	PCCP1	PCCP2	PCCP3	PCCP4
Conductivity	uS/cm		< 500		

Monitoring ,corrective action and responsibility:

CCP	Risk factor	source	Controlling options	Critical limit	Surveillance			Corrective Action	
					Procedure	Frequency	Responsibilit	Procedure	Responsibilit
P1	Hardness	Softener	Function of resin	1000ppm CaCo3	Sampling & analysis	Every morning	technician	Replacion exchanger	Technical dept

Codex Decision Tree for Determination of CCP[13]:



7. Set of Documents	
User Requirement Specification	Utilities Consumptions
Validation Master Plan	Material Certificates
Standard Operation Procedures	Welding Qualifications
Quality Inspection	Training Certificates
Functional Design Specification	Operating and Maintenance Manuals.
Process & Instrument Diagram	Recommended Spares Parts List
Valve Schedule	Design Change Control
Design Qualification	Process/Sequence Flow Diagrams
Software Design & Test Specification	Instrument/Equipment Location Drawings
Hardware Design & Test Specification	Calibration Certificates for Instruments,
Good Automated Manufacturing Practice	Calibration Certificates for Instruments used to Test Equipment
Factory Acceptance Test	Utilities Consumptions
Site Acceptance Test	General Arrangement Drawing
Installation Qualification	Detailed Design and Production Programme
Commissioning Protocol	
Operation Qualification	
Performance Qualification	

CALIBRATION CERTIFICATES *must be traceable back an internationally recognized authority.*

VII. CONCLUSION

Using of chlorine in the feed water tank provides a practical method for disinfection. Chlorine could be removed by SMBS to save the system membranes from corrosion. Treatment system using reverse osmosis followed by continuous electro deionization produces water of a satisfied quality and having an economical and practical advantages and avoiding the excessive use of chemicals. Control systems including UV, conductivity meter, TOC analyzer, Chlorine analyzer, heat exchangers, recirculation logic control provides a satisfied measures to control the chemical and microbiolgical quality attributes of purified water. Qualified performance requires proper risk analysis practice by determination of the critical control points to assess the quality attributes.

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