PROTOCOL

FOR

PERFORMANCE QUALIFICATION (PQ)

OF

PURIFIED WATER GENERATION, STORAGE AND DISTRIBUTION SYSTEM

PLANT LOCATION:XXXXXXXXX

Document No.	
Supersedes	
Effective Date	
Review Date	
No. Of Pages	
Reference Protocol No.	

COMPANY NAME
ADDRESS

PROTOCOL CONTENTS

Title: Protocol for Performance Qualification of Purified Water Generation, Storage and Distribution System

Protocol No.:XXXXXXXXXX	Effective Date:

1.0 Protocol Approval

This is a specific protocol for Performance Qualification of purified water generation, storage and distribution system.

This protocol has been approved by the following:

	Name	Department	Signature	Date
Prepared By				
Checked By				
Approved By				

Final Approval:

Final approval has been given by the following:

	Name	Signature	Date
Approved By (Plant Head)			
Approved By (Head – QA)			

2.0 Overview

2.1 Objective:

To establish the methodology for the performance qualification of purified water system, which is used for generation, storage and distribution of purified water in solid oral and liquid oral block including quality control Department.

2.2 Purpose and Scope

The purpose of this protocol is to provide a documentary evidence for the performance qualification of the water system:

- To ensure that purified water meets the Pharmacopoeial specifications of IP and USP.
- To confirm the appropriateness of critical parameters of the water system components.
- To perform purified water drain time study during sampling.
- To perform hold time study for stored purified water in the water storage tank.
- To establish reliability of water system.
- To finalize operating SOPs of water system.
- To establish Alert and Action levels.
- To establish the efficacy of sanitization procedures.
- To validate the system and check its performance for one year in order to cover all the seasonal variations.

This protocol is applicable to purified water generation, storage and distribution system, ***Equipment Tag No.____***

2.3 Responsibility

- **Protocol / Report Preparation:** Quality Control Executive, Quality Assurance Executive and Engineering Executive
- **Approval of Protocol / Report:** Quality Assurance Manager / Head-Quality Assurance
- **Execution of Qualification Activity:** Quality Control Executive, Service Engineer

2.4 Qualification Team:

- Quality Control Executive / Manager
- Project Executive / Manager
- Validation Manager
- Quality Assurance Manager

3.0 Training Record

3.1 Purpose

The purpose of the training is to familiarize the trainees with the principle of working & technical specifications of water system as well as overall strategy of Performance Qualification of the Water System.

3.2 Scope

This Training is related to the purified water generation, storage and distribution system and being imparted to the people involved in the water system validation.

3.3 Topics

The following topics shall be covered during training:

- Principle of working of water system.
- Technical specifications of the system components.
- Overall strategy of Qualification process.
- General precautions / guidelines to be followed during qualification.

Note: -

- ***Training shall be given as per SOP Title: _____ SOP No.: _____.***
- ***Training record shall be attached with the report as Annexure-01***

4.0 Pre – Qualification Requirements

Following instruments shall be required for the performance qualification of purified water generation, storage and distribution system.

Sr. No.	Equipment Name	Equipment Code / Sr. No.	Calibration Certificate No.	Calibration Due On
1.	pH Meter			
2.	TDS / Conductivity Meter			
3.	TOC Analyzer			

5.0 Performance Qualification Description

5.1 Generic Design

5.1.1 Introduction

United State Pharmacopoeia (USP29) recommends the following specifications for Purified Water (PW) in their monograph for Pharmaceutical Industry.

(a) pH : 5 – 7
(b) Conductivity : < 1.3 µS/ cm at 25 ° C (Stage-1 (On-line))
(c) TOC : < 500 ppb
(d) Total Bacterial Count: < 100 cfu / ml

Similarly Indian Pharmacopoeia (IP 1996) recommends the following specifications for Purified Water (PW) in their monograph for the pharmaceutical industry.

(e) Acidity / Alkalinity : To comply
(f) Ammonium Ions : To comply
(g) Ca^{2+} / Mg^{2+}Ions : To comply
(h) Heavy Metals : NMT 0.1 ppm
(i) Nitrate : To comply
(j) Chloride : To comply
(k) Sulphate : To comply
(l) Oxidisable substances : To comply
(m) Residue on Evaporation : NMT 1mg (0.001%)
(n) Total Bacterial Count : < 100 cfu / ml

However, the water system has been designed considering USP-29 and IP 1996 specifications, as the basis of maximum allowable parameters at each user point, along-with suitable Design Limits, Alert Limits and Action Limits.

5.1.2 System design details

The water system design has the following major stages of purification, distribution and control.

a) Pre-treatment System for Filtration and softening of raw water to produce soft water / potable water.

b) Generation System for Purified Water (using UF-RO-EDI system)

c) Storage and Distribution System for Solid Oral Block

d) Storage and Distribution System for Liquid Oral Block

e) Programmable Logic Control for pre-treatment, generation and distribution loop system.

5.1.3 Pre-treatment

The objective of pre-treatment is to treat raw water and produce feed water (within the limit of potable water / soft water) for the final purification system.

Water, used as feed water for the preparation of Purified Water, must meet the drinking water specifications. Therefore, pre-treatment of the raw water is equally important, as it is designed to produce water complying with pharmacopoieal specifications for drinking water. This reduces the load on the final purification system and maximizes the efficiency of the final purification stage.

The raw water is stored in the Day Storage tank. The raw water may have suspended solids, dissolved impurities, colloids, organics, bacterial impurities, etc. All these impurities may foul the RO membranes / any filters being used down stream. Hence, it is desirable to reduce the impurities to a specified level by pre-treatment.

Following treatments steps have been designed in the pre-treatment stage to produce soft water:

5.1.3.1 Chlorine Dosing System

Online Chlorine Dosing (Chlorine Dosing) has been provided, to disinfect the feed water as well as control the microbial contamination levels. Chlorine Dosing is done by addition of Sodium hypochlorite at a concentration of 3-6 mg / Litre. Free chlorine is normally maintained at a level of about 0.1 – 0.3 ppm. However, the concentration of chlorine level may be adjusted, on the basis of microbiological contamination in feed water.

Free chlorine in water also reduces the possibility of bacterial germination in the Multi grade Filter and Softener stages, which are otherwise potential breeding grounds for bacteria.

5.1.3.2 Multi grade Filter

Multi grade Sand Filter has been installed, which is having multiple layers of pebbles, gravels and sand. The Coagulated suspended particles, formed due to addition of chemicals in earlier steps, are removed from the raw water. This treatment also reduces silica and other suspended particles from the raw water.

5.1.3.3 Softener Unit

Two Softener units have been provided in the pre-treatment stage, in order to reduce the hardness of water to <5ppm.

These two softener columns work alternately, in order to provide a continuous flow of water, during regeneration of either one of the columns. Each softener column is regenerated in approximately 10 hrs. During regeneration of Softener - 1, the water is diverted to Softener – 2 by the operation of pneumatically operated valves.

The soft water, generated by the softener, is stored in a “Soft water Storage Tank”, in order to provide the necessary buffer required for the daily usage.

A minimum level of chlorine (NMT 0.5 ppm) is maintained, in the “soft water storage tank” during the process, to minimize the bacterial growth in the softener bed.

5.1.3.4 Soft Water Storage Tank

The “soft water”, generated by softener, is stored in “Soft water Storage Tank”. This tank has been provided with “water level transmitters” to monitor the water level in the tank.

The soft water is further supplied to the plant, for Utility Applications, through soft water transfer pump.

5.1.4 Generation system for Purified Water

The objective of generation system is to provide the purified water to the Purified Water Storage tank on demand before the same is distributed to the final user points by means of appropriate piping in the plants.

The soft water is passed through "activated carbon filter" (ACF) for the removal of chlorine, BOD and COD. ACF filtered water is further passed through micron cartridge filter, UV column and ultra-filtration system, for removal of suspended particles and microbial contamination. The UF-treated water of ultra filtration system is stored in SS tank.

The purified-water generation system is designed with "double-pass RO-system" and "EDI-system" for removal of dissolved salts. The RO-EDI treated water is further pass through a "UV column", to control the microbial growth in treated water. The UV-column treated-water, which qualifies USP/IP specifications for purified water, is transferred to the "purified water storage tanks for Solid Oral Block and Liquid Oral Block respectively.

Following treatments steps have been designed in the generation stage:

5.1.4.1 Activated Carbon Filter

Activated carbon filter removes free chlorine, as well as colour / odour, BOD & COD etc. from the soft water, to safe guard RO membranes. ACF has been provided as an add-on safety feature, for removal of BOD / COD from feed water.

5.1.4.2 Micron Cartridge Filter

Suspended particulates in feed-water may choke the UF-membrane passage and may also damage the UF-membranes, thus affecting performance & life of UF-system.

A 5-micron cartridge filter removes the suspended particulates from the feed water.

Pressure Gauges across the "5-micron cartridge filter" have been provided, in order to identify the choking of cartridge filter and facilitate its replacement. The 5-micron cartridge filter has large surface area and may provide the breeding ground for microbial growth. Accordingly, the chlorinated water prevents the growth of microbial load. Free chlorine present in water prevents any microbial growth in 5-micron cartridge filter.

5.1.4.3 Ultra Violet System

A UV system has been provided at the Micron Cartridge Filter's outlet, as an additional safety measure, to control the microbial load in the Ultra Filtration system.

5.1.4.4 Ultra-filtration, Reverse Osmosis & Electro-Deionization System

5.1.4.4.1 Ultra-filtration System

Ultra-filtration (UF) system is used for removal of microbial contamination & COD etc.

Ultra-filtration system is a membrane separation process. It employs a cross flow path of water, across a membrane, where the purified-water & reject-water are separated out continuously. The reject-water, containing the separated bacteria, is continuously drained, thus avoiding the accumulation of bacteria in the purified-water.

The UF system is sanitized by using appropriate sanitizing chemicals. In addition, the UF system is periodically back-washed by using UF-permeate water / purified-water.

5.1.4.4.2 Anti-scalant Dosing System

The salts, precipitated during desalination process, tend to deposit on the RO-membrane surface, thus affecting the performance of RO-system. In order to avoid deposition of salts on RO-membranes, appropriate anti-scalant agent dosing is provided, which reduces salt-deposition & maximizes cleaning cycle interval for the RO-membranes.

5.1.4.4.3 pH Correction Dosing System

Appropriate pH correction dosing system (for pH correction of RO-feed-water) has been provided in order to maintain the quality of RO-permeate water. An alkaline pH ensures the removal of dissolved CO2 from the system during desalination. A pH controller pHC06-1101 monitors / controls the pH of the feed-water.

5.1.4.4.4 SMBS Dosing System

Free chlorine in the feed-water can damage the Polyamide RO membranes. Therefore free chlorine has to be removed from the feed-water. In the designed purification scheme, ACF removes free chlorine from the water.

However, additional safeguard system in the form of "SMBS dosing system" has been provided to ensure the safety of RO-membranes.

The free chlorine in soft water is effectively removed by dosing of sodium metabisulphite solution. In order to detect free chlorine, an online "chlorine analyser" has been provided, which opens the dump valve on sensing free chlorine, thereby dumping the water, till the chlorine levels in the feed-water are within permissible limits. The system is tripped if the chlorine is detected during normal operation to protect the RO membranes.

5.1.4.4.5 Micron Cartridge Filter

Suspended particulates in feed-water may choke the RO-membrane passage and may also damage the RO-membranes, thus affecting performance & life of RO-system.

A 5-micron cartridge filter removes the suspended particulates from the feed water.

Pressure Gauges across the "5-micron cartridge filter" have been provided, in order to identify the choking of cartridge filter and facilitate its replacement..

5.1.4.4.6 Buffer Tank

An on-line jacketed buffer tank , with electrical heating system in the jacket, has been provided at the inlet of "two pass RO-system". This tank is also used during hot water sanitization or chemical cleaning of the RO-membrane. Since the tank is in-line during the operation, this arrangement reduces the possibility of bio-film formation in the tank , during stagnation or idle conditions.

5.1.4.4.7 Two Pass Reverse Osmosis System

The pre-treated water is further passed through "Reverse Osmosis (RO) Module" for primary salt reduction from the soft water.

Reverse Osmosis is the process, which removes the dissolved salt molecules by filtration through polyamide semi-permeable membranes. The RO-system operates above the osmotic pressure, thereby facilitating reverse osmosis and reduction of salt content by 90-95%.

Reverse Osmosis also removes suspended particulates and reduces total organic carbon (TOC) present in the feed-water.

The RO system can reduce total dissolved solids (TDS) in the permeate-water to levels, which are less than 100 ppm.

5.1.4.4.8 Second Pass RO System

The RO-permeate water is then passed through second pass of RO-membranes, for further reduction of TDS, suspended particulates & TOC. The second pass RO-system can reduce TDS in permeate water to levels less than 20ppm.

The RO system has been designed for periodic sanitization with hot water.

5.1.4.4.9 Electro-Deionization System

The RO-permeate water is further subjected to Electro-deionization process to bring down the overall conductivity < 1.0 micro-siemens/cm.

Since RO-system is not sanitary in construction, the RO-permeate water may have some ionic load during prolonged operation.

The RO-permeate water is therefore treated with Electro-deionization (EDI) process to remove ionic load and reduce conductivity.

The EDI is either back-flushed with permeate water or chemically sanitized, if it becomes necessary, as per Supplier recommended procedures.

5.1.4.4.10 Ultra Violet System

A UV system has been provided at the EDI outlet, as an additional safety measure, to control the microbial load in the Purified water. Thus the water coming at outlet is characterized as 'Purified Water' and tested against the USP29/IP1996 specifications of Purified Water.

5.1.5 Storage And Distribution System Description

The purified water, generated by water system, is fed to the "purified water storage tanks, on demand, prior to the distribution to final user points. The storage tanks capacities have been arrived at, keeping in mind the peak load & buffer volumes to be maintained.

The purified water, stored in the "purified water storage tanks, is supplied to various usage points in the plant, by means of a piping/distribution network, which is a "closed loop system". The water piping/distribution system is being maintained at ambient temperature.

UV Column : Since the water distribution system is being maintained at ambient temperature, therefore 'bacterial load control' will be of major concern. Bacterial load control is being taken care off by an "online UV column", which is installed in the "water distribution loop" prior to its distribution to the user points.

An "intensity monitor" along-with an "online sensor and panel mounted monitor" has also been installed, which will monitor the intensity of the UV-tubes, at any instance and facilitate their replacement at appropriate frequency.

Conductivity Sensor : The quality parameters of purified-water system, such as conductivity, are continuously monitored and provide necessary control for the water system operation. In case of any deviation in the water quality, "necessary tripping/alarm" are triggered, in order to draw the attention of the system operator. For this purpose, an "online conductivity sensor" has been installed, which can actuate a drain / dump valve (on deviation from set limits) and prevent purified water from being distributed to the user points. This safeguards the users from using poor quality water.

Purified Water Storage Tanks:

The "purified water storage tanks have been designed as jacketed tanks, for heating with steam during sanitization. The sanitization is performed by activating a steam control valve, which is controlled by an "online temperature controller" for maintaining the water distribution systems at an elevated temperature for a stipulated period of time.

For safe working of the water system, "water level controllers" have been provided in the storage tanks, which prevent the tanks from overflowing as well as safeguard the pumps from running dry. In case of high water level in storage tank, water can be diverted to the process water tank.

Purified Water Distribution Loops:

Two separate loops have been provided, for Solids oral & Liquid oral blocks. Both the loops are identical in design and basic control systems, but are designed for the agreed user requirements for respective loops.

5.1.5.1 Storage & Distribution System for Solid Oral Block:

The storage & distribution of purified water, for Solid Oral Block, is designed with a closed loop system. All the user points, in the Solid Oral Block, have been provided with a zero dead leg valve. Also a minimum velocity of water is maintained in the entire loop. Storage and Distribution system have been designed as per the guidelines of ISPE for minimum velocity in the loop as well as turn over in storage tank etc. The purified water storage tank has been designed as a steam-jacketed tank, to facilitate periodic sanitization of the entire loop, using hot water.

5.1.5.2 Storage & Distribution System for Liquid Oral Block:

The storage & distribution system of purified water, for Liquid Oral Block, is similar in design and configuration / controls to the Solid Oral Block, However, the entire system has been dedicatedly designed to meet the Liquid Oral Block requirement.

5.1.5.3 Programmable Logic Control for pre-treatment, generation and distribution loop system.

Separate PLC / panels have been provided for pre-treatment stages, UF-RO-EDI stages of purified water generation, as well as for storage & distribution system for solid and liquid oral blocks.

Pre-treatment plant has been provided with a separate PLC system and a man machine interface (MMI) on the control panel, located in the pre-treatment block. All the necessary interlocks / controls are monitored by PLC for the operational status.

Purified water generation and distribution systems have been provided with separate PLC and MCC panels. The control panel is provided with 10-inch touch screen MMI for plant operations. The plant people can also access the system for operation and data acquisition, using supervisory control as per design.

5.1.5.4 Test Programme:

The Performance Qualification of water system shall be carried out in three phases:

(a) Phase-1 – extensive sampling from Generation points & usage points for 4 weeks

(b) Phase-2 – extensive sampling from selective generation & all usage points for 3 months

(c) Phase-3 – routine sampling from usage points on rotation basis, for 8 months

The detailed methodology of the 3 phases of validation is as given below:

Phase - 1: (For a period of 4 weeks / 28 days)

The performance qualification of water system shall be started, when all the equipment and piping of water system have been verified to be installed properly and are operating correctly.

Phase-1 of the performance qualification of water system shall include extensive sampling of water, from various points in the pre-treatment system and purified water generation system along with all the usage points of the distribution loops (as described in sec. 5.6). The phase-1 sampling shall be carried out for a period of 4 weeks.

During this phase water samples from the chosen generation / usage points shall be analyzed and monitored for compliance to the pre-determined specifications (as described in the section 5.4).

After successful completion of Phase-1 of the performance qualification, the Purified Water system shall be cleared for usage of Purified water in manufacturing operations. Purpose of Phase-1 qualification is to stabilize the operating parameters and develop the cleaning / sanitization procedures / sanitization frequencies / sampling methods / drain time study and hold time study. Conclusions shall be described in a summary report.

During Phase-1, water samples shall also be collected for drain time study and hold time study. The following procedure shall be followed for drain time & hold time study:

- **Drain Time Study:**

Drain time study for purified water shall be done during **Ist phase**. Samples shall be drawn from the last user point considering the worst case on every weekend for first three weeks. Samples shall be collected at 0, 5 & 10 minutes while the cork is open and shall be checked for bio burden as per the specifications of purified water.

- **Hold Time Study:**

Hold time study for purified water shall be done during **Ist phase**. Samples shall be drawn from the last user point considering the worst case on every weekend for first three weeks. Purified

water shall be collected and kept in the container and sample shall be withdrawn at 0, 1, 3, 5, 8 & 12 hours. Samples shall be checked for bio burden as per the specifications of purified water.

Phase – 2: ***(For a period of 3 months)***

Phase-2 of the performance qualification shall commence, after successful completion of Phase-1. Purpose of Phase-2 qualification is to monitor the operating parameters as well as cleaning / sanitization procedures / sanitization frequencies / sampling methods. The objective of Phase-2 is also to demonstrate that system will produce desired quality of water, on a consistent basis, when operated in conformance with SOP established at the end of Phase-1. Conclusions shall be mentioned in Summary report.

During Phase-2, water samples shall be collected from all the Sampling Points and Usage Points on a Daily basis (Sampling plan mentioned in 5.6). Phase-2 of the performance qualification of water system shall include extensive sampling of water, from end points in the purified water generation system (as described in sec. 5.4.2) & all the usage points of the distribution loops (as described in sec. 5.4.3), daily. Phase-2 sampling shall be carried out for a period of 3 months. Water samples from the all the chosen usage points shall be analyzed and monitored, daily, for compliance to the pre-determined specifications (as described in the section 5.5).

After successful completion of Phase-2 of the performance qualification, the Purified Water system shall be cleared for Phase-3.

Phase – 3: ***(For a period of 8 months)***

Phase-3 shall commence immediately after completion of Phase-2. The objective of Phase-2 is to demonstrate that the water system is capable of producing consistent quality water, by taking care of all possible seasonal variations, when operated in accordance with the established SOP's over a long period of time. The sampling shall be done as per the routine sampling procedures. Samples shall be collected from selected Sampling points once a week and shall randomly cover all User points in a week. (Sampling plan mentioned in 5.7). When the third phase is completed data shall be collected

After Phase-3 routine monitoring schedule shall be frozen.

Definition:

Sampling points: All the sample collection points of pre-treatment (MGF – Softener) and generation system of purified water (ACF – UF – RO – EDI) prior to Distribution loop systems termed as sampling points.

Usage points: All the sampling points on distribution loop systems for Oral Solid block and Oral Liquid, QC block are termed as Usage points.

5.2 Required Water Specifications

5.2.1 Specification of Raw Water:

S. No.	Test Parameter	Specification	STP code
1.	Description	Clear colourless, odourless and	

		tasteless liquid	
2.	pH	Between 5.0 to 8.0	
3.	Total Dissolved Solids	To record results	
4.	Hardness	To record results	
5.	Chlorides	To record results	
6.	Sulphates	To record results	
7.	Total Microbial Count	NMT 500 cfu / ml	
8.	Pathogens a) *Escherichia coli* b) *Salmonella* c) *Pseudomonas aerugonisa* d) *Staphylococcus aureus*	 Should be absent Should be absent Should be absent Should be absent	
9.	Enterobacteriaceae	Should be absent	

5.2.2 Specification of Potable Water:

S. No.	Test Parameter	Specification	STP code
1.	Description	Clear colourless, odourless and tasteless liquid	
2.	Total Microbial Count	NMT 500 cfu / ml	
3.	Pathogens a) *Escherichia coli* b) *Salmonella* c) *Pseudomonas aerugonisa* d) *Staphylococcus aureus*	 Should be absent Should be absent Should be absent Should be absent	
4.	Enterobacteriaceae	Should be absent	

5.2.3 Specification of Soft Water:

S. No.	Test Parameter	Specification	STP code
1.	Description	Clear colourless, odourless and tasteless liquid	
2.	pH	Between 5.0 to 8.0	
3.	Total Dissolved Solids	To record results	
4.	Hardness	To record results	
5.	Total Microbial Count	NMT 500 cfu / ml	
6.	Pathogens *a) Escherichia coli* *b) Salmonella* *c) Pseudomonas aerugonisa* d) *Staphylococcus aureus*	 Should be absent Should be absent Should be absent Should be absent	

5.2.4 Specification of RO treated Water:

S. No.	Test Parameter	Specification	STP code
1.	Description	Clear colourless, odourless and tasteless liquid	
2.	pH	Between 5.0 to 7.5	
3.	Calcium and Magnesium	A pure blue colour is produced	
4.	Heavy Metals	Comply as per I.P.	
5.	Total Microbial Count	NMT 100 cfu / ml	
6.	Pathogens *a) Escherichia coli* *b) Salmonella* *c) Pseudomonas aerugonisa* d) *Staphylococcus aureus*	 Should be absent Should be absent Should be absent Should be absent	

5.2.5 Specification of Purified Water:

S. No.	Test Parameter	Specification	STP code
1.	Description	Clear, colourless, odourless and tasteless liquid.	
2.	pH	Between 5.0 to 7.0	
3.	Chlorides	The solution does not show any change in appearance at least after 15 minutes.	
4.	Sulphates	The solution does not show any change in appearance at least after 1 hour.	
5.	Nitrates	Comply as per I.P.	
6.	Ammonium	Test solution is not more intensely coloured than standard solution.	
7.	Calcium &Magnesium	Pure blue colour is produced.	
8.	Heavy Metals	Comply as per I.P.	
9.	Residue on Evaporation	Not more than 0.001%	
10.	Acidity or Alkalinity	The solution is not red and blue coloured.	
11.	Conductivity	Not more than 2.1 µs/ cm at 25°C	
12.	Oxidisable substances	The solution remains faintly pink.	
13.	Total Organic Carbon	Not more than 500 ppb	
14.	Total Microbial Count	Not more than 100 cfu / ml	
15.	Pathogens a) *Escherichia coli* b) *Salmonella* c) *Pseudomonas aerugonisa* d) *Staphylococcus aureus*	 Should be absent Should be absent Should be absent Should be absent	

5.3 Test Specification, Sampling Plan & Frequency

S. No.	Name of the Sampling point	Specification Compliance	Sampling point No.	Room No.	Phase – 1 Sampling frequency	Phase – 2 Sampling frequency	Phase – 3 Sampling frequency / Day
A	**Sampling points in Pre-treatment system**						
1.	Raw water inlet	Raw Water	SP001	NA	Daily	Weekly	Weekly
2.	Inlet of Multi grade Filter	Raw Water	SP002	NA		NA	NA
3.	Outlet of Multi grade Filter	Potable Water	SP003	NA		NA	NA
4.	Outlet of Softener Plant – 1	Soft water	SP004	NA		NA	NA
5.	Outlet of Softener Plant - 2		SP005	NA		NA	NA
6.	Outlet of Soft water Storage tank		SP006 A / B / C / D	NA		NA	NA
B	**Sampling points in Generation system**						
7.	Inlet of Activated Carbon Filter	Soft water	SP007	NA	Daily	Weekly	Weekly
8.	Outlet of Activated Carbon Filter		SP008	NA		Weekly	Weekly
9.	Inlet of Micron Cartridge Filter		SP009	NA		NA	NA
10.	Out let of Micron Cartridge Filter		SP010	NA		NA	NA
11.	Outlet of Ultra violet system (Before UF)		SP011	NA		Weekly	Weekly
12.	Outlet of Ultra Filtration System		SP012	NA		Weekly	Weekly
13.	Out let of Storage Tank		SP013	NA		NA	NA
14.	Outlet of Anti scalant dosing system		SP014	NA		NA	NA
15.	Outlet of pH correction dosing system		SP015	NA		NA	NA
16.	Out let of Micron Cartridge Filter		SP016	NA		NA	NA

S. No.	Name of the Sampling point	Specification Compliance	Sampling point No.	Room No.	Phase – 1 Sampling frequency	Phase – 2 Sampling frequency	Phase – 3 Sampling frequency / Day
17.	Outlet of SMBS dosing system	Soft water	SP017	NA	Daily	NA	NA
18.	Permeate of RO Module - 1	RO Treated water	SP018	NA		Weekly	Weekly
19.	Permeate of RO Module - 2		SP019	NA		Weekly	Weekly
20.	Permeate of EDI - 1	RO Treated water	SP020	NA		Weekly	Weekly
21.	Permeate of EDI - 2		SP021	NA		Weekly	Weekly
22.	Outlet of Ultra Violet System (After EDI)	Purified Water	SP022	NA		NA	NA
C	**Sampling points/Usage points in Distribution loop system for Oral solids block**						
23.	Outlet of Pump	Purified Water	SP023	NA	Daily	Daily	Monday
24.	Outlet of Ultra Violet System		SP024	NA			Tuesday
25.	Return loop of distribution system for Oral solids		SP025	NA			Wednesday
26.	Bin Wash		xxxx	T – 02			Monday
27.	Area-1		xxxx	T – 23			Monday
28.	Area2		xxxx	T – 23A			Monday
29.	Area-3		xxxx	T – 26			Tuesday
30.	Area-4		xxxx	T – 26A			Tuesday
31.	Area-5		xxxx	T – 30			Tuesday
32.	Area-6		xxxx	T – 30A			Wednesday
33.	Area-7		xxxx	T – 36			Wednesday
34.	Area-8		xxxx	T – 36A			Wednesday
35.	Area-9		xxxx	T – 41			Thursday

S. No.	Name of the Sampling point	Specification Compliance	Sampling point No.	Room No.	Phase – 1 Sampling frequency	Phase – 2 Sampling frequency	Phase – 3 Sampling frequency / Day
36.	Area 10	Purified Water	xxxx	T – 41A	Daily	Daily	Thursday
37.	11		xxxx	T – 48			Thursday
38.	12		xxxx	T – 49			Thursday
39.	13		xxxx	T – 52			Friday
40.	14		xxxx	T – 52A			Friday
41.	15		xxxx	T – 90			Friday
42.	16		xxxx	T – 91			Friday
43.	17		xxxx	T – 92			Saturday
44.	18		xxxx	T – 98			Saturday
45.	19		xxxx	SG – 28			Monday
46.	20		xxxx	SG – 26			Tuesday
47.	21		xxxx	SG – 27			Wednesday
48.	22		xxxx	SG – 22			Thursday
49.	23		xxxx	NA			Friday
50.			xxxx	NA			Saturday
D	**Sampling points /Usage points in Distribution Loop System for Liquid Oral and QC Block**						
51.	Outlet of Pump	Purified Water	xxxx	NA	Daily	Daily	Monday
52.	Outlet of Ultra Violet System		xxxx	NA			Tuesday
53.	Return loop of distribution system for Liquid Oral and QC Block		xxxx	NA			Wednesday
54.	Wash		xxxx	L – 05			Monday
55.	Syrup Mfg.		xxxx	L – 10			Monday

S. No.	Name of the Sampling point	Specification Compliance	Sampling point No.	Room No.	Phase – 1 Sampling frequency	Phase – 2 Sampling frequency	Phase – 3 Sampling frequency / Day
56.	Wash	Purified Water	xxxx	L – 13	Daily	Daily	Monday
57.	Preparation		xxxx	L – 17			Monday
58.	Preparation		xxxx	L – 17			Tuesday
59.	Preparation		xxxx	L – 19			Tuesday
60.	Preparation		xxxx	L – 19			Tuesday
61.	Mfg. – 3		xxxx	L – 21			Tuesday
62.	Mfg. – 3		xxxx	L – 21			Wednesday
63.	Wash		xxxx	L – 22			Wednesday
64.	Mfg. – 2		xxxx	L – 24			Wednesday
65.	Mfg. – 2		xxxx	L – 24			Wednesday
66.	Mfg.		xxxx	L – 27			Thursday
67.	Wash		xxxx	L – 28			Thursday
68.	Hold		xxxx	L – 29			Thursday
69.	Hold		xxxx	L – 29			Thursday
70.	Fill / Seal		xxxx	L – 39			Friday
71.	Fill / Seal		xxxx	L – 43			Friday
72.	Fill / Seal line – 3		xxxx	L – 48			Friday
73.	Fill / Seal line – 2		xxxx	L – 52			Friday
74.	Fill / Seal line – 1		xxxx	L – 56			Saturday
75.	QC Wash room		xxxx	NA			Saturday
76.	Microbiology Lab		xxxx	NA			Saturday
77.	Microbiology Lab		xxxx	NA			Saturday

5.4 Required SOP's

The water system operation will be carried out as per given SOPs:

a) Operation of Water System (SOP No.: _____).

b) Preparation of Sodium hypochlorite solution (SOP No.: _____).

c) Preparation of Anti-scalant solution (SOP No.: _____).

d) Cleaning of Cartridge filters (SOP No.: _____).

e) Cleaning of UV purifier and replacement of UV lamps (SOP No.: _____).

f) Regeneration procedure for Softener (SOP No.: _____).

g) Sanitization Procedure on Distribution loop system (SOP No.: _____).

The program involves intensive daily sampling and testing of major process points at "Normal Operating Conditions."

In the process, regeneration, sanitization procedure and storage period of water in the storage tank shall be established.

5.5 Evaluation of Results

Phase - 1 Result

After completion of Phase-I, Alert and Action limits of testing parameters for purified water will be calculated as per given equation and these alert and action limits will be followed for further qualification of water system.

Alert levels are levels or range that, when exceeded; indicate that a process may have drifted from its normal operating condition.

Alert levels constitute a warning and do not necessarily require a corrective action.

"Alert Level = Average + 2 X Standard Deviation"

Action levels are levels or range that, when exceeded, indicate that a process has drifted from its normal operating range. Exceeding an Action level indicates that corrective action should be taken to bring the process back into its normal operating range).

"Action Level = Average + 3 X Standard Deviation"

- Based on the Study of Drain time, conclusion will be drawn for the period of drainage of Purified Water before usage during process.
- Based on Hold Time study, conclusion will be drawn for Purified Water storage period in case it is required.

Phase – 2 Results

After successful completion of Phase – 2, frequency of regeneration, sanitization operation shall be finalized. The frequency obtained during Phase – 2 studies shall be followed in Phase – 3.

Phase – 3 Results

After successful completion of Phase – 3, data obtained during the process shall be compiled and conclusion shall be drawn considering the Seasonal variation factor. Thereafter Purified Water Generation Storage and Distribution System shall be released for regular usage.

6.0 Performance Qualification Procedure

The following procedure shall be used for performance qualification of purified water generation, storage and distribution system:

6.1 Ensure that water system has qualified for operational qualification.

6.2 Sanitization shall be performed as per respective SOP. The observation of the study shall be recorded as per the format provided in Exhibit-01. The data sheets shall be attached date wise in Annexure-01.

6.3 The phase-1 studies shall be done as per point no.5.5. The observations of the study shall be recorded as per the format provided in Exhibit-02 to Exhibit-08. The data sheets shall be attached date wise in Annexure-02. After completion of phase-I studies the graphical representation of the data of all the parameters shall be done individually and attached in Annexure-03.

6.4 The phase-2 studies shall be done as per point no.5.6. The observations of the study shall be recorded as per the format provided in Exhibit-02 to Exhibit-06. The data sheets shall be attached date wise in Annexure-04. After completion of phase-2 studies the graphical representation of the data of all the parameters shall be done individually and attached in Annexure-05.

6.5 The phase-3 studies shall be done as per point no.5.7. The observations of the study shall be recorded as per the format provided in Exhibit-02 to Exhibit-06. The data sheets shall be attached date wise in Annexure-06. After completion of phase-1 studies the graphical representation of the data of all the parameters shall be done individually and attached in Annexure-07.

6.6 Any deviation observed in performance qualification shall be recorded as observed deviation, corrective action and justification report.

6.7 Observed deviation shall be reported to the Quality control - Head and Quality Assurance – Head.

6.8 If the observed deviation does not have any major impact on the qualification the final conclusion shall be provided.

6.9 If the observed deviation has major impact on the qualification, deviation shall be reported to the manufacturer for the corrective action and qualification activity shall be redone.

7.0 Acceptance Criteria

Performance qualification shall be considered acceptable when requirements listed in section 6.0 of this protocol have been fulfilled and all the components of

purified water generation, storage and distribution system are performed as per the design specifications and as per manufacturer recommendations.

8.0 Qualification Report

The performance qualification report shall consist of a summary document, in narrative form, which shall briefly describe the activity performed along with the observations recorded in relevant exhibits.

This report shall also include the related documents and attachments / annexure which were completed at the time of qualification activity.

9.0 Approval of Qualification Report

The report shall be evaluated and proper references / conclusions / recommendations shall be recorded by Quality Assurance.

The performance qualification report shall be evaluated and finally approved by quality assurance.

10.0 Observed Deviation

Sr. No.	Page No.	Point No.	Observed Deviation	Deviation Reported By	Deviation Approved By	Corrective Action Taken	Justification of Corrective Action	Corrective action taken and justification given by	
Report Approved By									
Department Head						**Quality Head**			

11.0 List of Exhibits / Annexure

11.1 List of Exhibits

Exhibit No.	Exhibit Title	No. of Pages
01	Data sheet for PQ test results of Raw water	
02	Data sheet for PQ test results of Potable water	
03	Data sheet for PQ test results of Soft water	
04	Data sheet for PQ test results of RO water	
05	Data sheet for PQ test results of Purified water	
06	Data Sheet for Study the Regeneration and Sanitization schedule of Pre-treatment, Generation and Distribution System by monitoring Microbial Data	
07	Data Sheet for Drain Time Study Test Results of Purified Water	
08	Data Sheet for Hold Time Study Test Results of Purified Water	

11.2 List of Annexures

Annexure No.	Annexure Title	No. of Pages
01	Record for Sanitization	
02	Data sheets of Phase-I	
03	Graphical representation of Phase-I results	
04	Data sheets of Phase-II	
05	Graphical representation of Phase-II results	
06	Data sheets of Phase-III	
07	Graphical representation of Phase-III results	
08	Report for Performance Qualification of Water system	

12.0 Reference Documents

12.1 Design Qualification (Doc No.: DIECIL – 62 – Q02 – 00).

12.2 Installation Qualification ( )

12.3 Operation Qualification ( )

12.4 United States Pharmacopoeia (USP29).

12.5 Indian Pharamcopoeia (IP1996).

Exhibit – E01

Data Sheet for Study the Regeneration and Sanitization schedule of Pre-treatment, Generation and Distribution System by monitoring Microbial Data

System Name:

Tag No.:

Sampling Point No.:
Phase:

Date	Microbial Load		Regeneration/ Sanitization Date	Microbial Load	
	Total Microbial Count	Pathogens		Total Microbial Count	Pathogens

Sampled By : _____

Analysed By : _____

Checked By : _____

Exhibit – E02

Data Sheet for PQ Test Results of Raw Water

System Name:

Tag No.:

Sampling Point No.:
Phase:

Date (➔)								
Test Parameters (🡻)		**Results**						
Description								
pH								
Total Dissolved Solids								
Hardness								
Chlorides								
Sulphates								
Total Microbial Count								
Pathogens	*Escherichia coli*							
	Salmonella							
	Pseudomonas aeruginosa							
	Staphylococcus aureus							
Sampled By	Chemical Analysis							
	Microbiological Analysis							
Analysed By	Chemical Analysis							
	Microbiological Analysis							
Checked By								

Approved By:

Date:

Exhibit – E03

Data Sheet for PQ Test Results of Potable Water

System Name:

Tag No.:

Sampling Point No.:
Phase:

Date (➔)								
Test Parameters (🡻)		**Results**						
Description								
Total Microbial Count								
Pathogens	*Escherichia coli*							
	Salmonella							
	Pseudomonas aeruginosa							
	Staphylococcus aureus							
Enterobacteriaceae								
Sampled By	Chemical Analysis							
	Microbiological Analysis							
Analysed By	Chemical Analysis							
	Microbiological Analysis							
Checked By								

Approved By:

Date:

Exhibit – E04

Data Sheet for PQ Test Results of Soft Water

System Name:

Tag No.:

Sampling Point No.:
Phase:

Date (➔)								
Test Parameters (🡻)		**Results**						
Description								
pH								
Total Dissolved Solids								
Hardness								
Total Microbial Count								
Pathogens	*Escherichia coli*							
	Salmonella							
	Pseudomonas aeruginosa							
	Staphylococcus aureus							
Sampled By	Chemical Analysis							
	Microbiological Analysis							
Analysed By	Chemical Analysis							
	Microbiological Analysis							
Checked By								

Approved By:

Date:

Exhibit – E05

Data Sheet for PQ Test Results of RO Treated Water

System Name:

Tag No.:

Sampling Point No.:
Phase:

Date (➔)								
Test Parameters (🡻)		**Results**						
Description								
pH								
Calcium & Magnesium								
Nitrates								
Heavy Metals								
Total Microbial Count								
Pathogens	*Escherichia coli*							
	Salmonella							
	Pseudomonas							
	Staphylococcus							
Sampled By	Chemical Analysis							
	Microbiological Analysis							
Analysed By	Chemical Analysis							
	Microbiological Analysis							
Checked By								

Approved By:

Date:

Exhibit – E06

Data Sheet for PQ Test Results of Purified Water

System Name:
Tag No.:
Sampling Point No.:
Phase:

Date (➔)								
Test Parameters (🡻)		**Results**						
Description								
pH								
Sulphates								
Nitrates								
Chlorides								
Ammonium								
Calcium & Magnesium								
Heavy Metals								
Residue on Evaporation								
Acidity or Alkalinity								
Conductivity								
Oxidisable substances								
Total Organic Carbon								
Total Microbial Count								
Pathogens	*Escherichia coli*							
	Salmonella							
	Pseudomonas aeruginosa							
	Staphylococcus aureus							
Sampled By	Chemical Analysis							
	Microbiological Analysis							
Analysed By	Chemical Analysis							
	Microbiological Analysis							
Checked By								

Approved By:
Date:

Exhibit – E07

Data Sheet for Drain Time Study Test Results of Purified Water

System Name:

Tag No.:

Sampling Point No.:
Phase:

Week (➔)						
Date (➔)						
Time (🡻)	**Results**					
Test parameters (➔)	Total Microbial Count	Pathogen	Total Microbial Count	Pathogen	Total Microbial Count	Pathogen
0 minutes						
5 minutes						
10 minutes						
Sampled By						
Analysed By						
Checked By						

Exhibit – E08

Data Sheet for Hold Time Study Test Results of Purified Water

System Name:

Tag No.:

Sampling Point No.:
Phase:

Week (➔)						
Date (➔)						
Time (🡻)	**Results**					
Test parameters (➔)	Total Microbial Count	Pathogen	Total Microbial Count	Pathogen	Total Microbial Count	Pathogen
0 hr						
1 hr						
3 hr						
5 hr						
8 hr						
12 hr						
Sampled By						
Analysed By						
Checked By						

Annexure – 01
Record for Sanitization

Equipment Name:	Purified water generation, storage and distribution system
Equipment Tag No.:	
Location:	xxxxxxxxxxxx
No. of Pages:	

Annexure – 02

Data Sheets of Phase-I

Equipment Name:	Purified water generation, storage and distribution system
Equipment Tag No.:	
Location:	xxxxxxxxxx
No. of Pages:	

Annexure – 03

Graphical Representation of Phase-I Results

Equipment Name:	Purified water generation, storage and distribution system
Equipment Tag No.:	
Location:	xxxxxxxxxx
No. of Pages:	

Annexure – 04
Data Sheets of Phase-II

Equipment Name:	Purified water generation, storage and distribution system
Equipment Tag No.:	
Location:	xxxxxxxxxxx
No. of Pages:	

Annexure – 05
Graphical Representation of Phase-II Results

Equipment Name:	Purified water generation, storage and distribution system
Equipment Tag No.:	
Location:	xxxxxxxxxxx
No. of Pages:	

Annexure – 06
Data Sheets of Phase-III

Equipment Name:	Purified water generation, storage and distribution system
Equipment Tag No.:	
Location:	xxxxxxxxxxxxx
No. of Pages:	

Annexure – 07

Graphical Representation of Phase-III Results

Equipment Name:	Purified water generation, storage and distribution system
Equipment Tag No.:	
Location:	xxxxxxxxx
No. of Pages:	

Annexure – 08
Report for Performance Qualification of Water system

Equipment Name:	Purified water generation, storage and distribution system
Equipment Tag No.:	
Location:	xxxxxxxxxxxxxx
No. of Pages:	