Risk Assessment Document

For

Purified Water Generation, Storage & Distribution System

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RISK ASSESSMENT FOR PURIFIED WATER GENERATION, STORAGE AND DISTRIBUTION SYSTEM

1 Introduction

According to the definition, given in Annex 15 to the EU-GMP-Guide, a Risk Assessment is a method to assess and characterize the critical parameters in the functionality of an equipment or process. Therefore, risk assessment is a key element in the qualification and validation approach.

In the project context, risk assessment for the equipment is performed as basic GMP/EHS-Risk Assessment, which shall help to identify important GMP/EHS-requirements.

2 Aim of Risk Assessment

At the very basic stage of design the Risk Assessment is carried out to verify that all features are taken into consideration to avoid the risk of failure of critical GMP and EHS parameter in the equipment.

During study, all GMP, EHS and operational parameters will be identified and assessed for the risk, appropriate mitigation will be proposed and verification point will be identified and defined.

The Risk Assessment report is produced to provide the documented evidence that design concepts or requirement are complete in considering all GMP, EHS and operational risks.

3 Reference Documents/Drawings

S.No.	Document Title	Document Number
1.	Validation master plan	

4 Equipment/ System Description

This risk assessment is conducted for a Purified Water Generation, Storage & distribution System, which shall consist of the following main components:

PW Generation system

The fully automatic PLC based purified water Generation system shall generate Purified water as per current USP.
The scheme of purified water generation system is as follows**:**

a). Pre treatment:

- NaOCl dosing system
- Raw Water Storage tank
- Raw Water Pump
- Multi Graded Filter
- Softener Unit
- Ultra Filtration
- UV Light
- UF Water Storage tank
- pH Correction Dosing system

- Anti-scalant Dosing System
- SMBS Dosing Tank
- 5 µm Micron Cartridge Filter
- pH meter
- ORP Analyzer along with auto-dumping valve

b). PW Generation System:

- RO High Pressure Pump
- Industrial RO with housing
- Conductivity Meter with alarm
- RO + EDI unit
- Conductivity Meter with alarm

c). Purified Water storage & Distribution system

- Purified Water Storage Tank
- Purified Water Transfer Pump
- TOC Analyzer
- Ultra Violet Lamp
- User Points
- Flow transmitter in supply & return line
- Temperature sensor in supply & return line
- Conductivity meter with auto-dumping facility

Storage tank

The size of the tank is based on the feed flow rate of the PW generation plant and the peak load of the user points. PW storage tank assembly consists of following components.

- Vertical Storage tank of SS316L, Internally electro polished.
- Level sensor (Magnetic type)
- Vent filter with electrically heated SS housing & temp. Indicator
- Spray balls
- Tank Drain Valve
- Sanitary Diaphragm Valves
- Compound pressure gauge

Distribution loop:

Distribution loop is fabricated out of SS 316L tubes and tube fittings (sanitary type). Distribution loop has user points, which are located at various locations in the Reagent manufacturing facility. All the user point valves shall be manual & Auto zero dead leg valve. Return line of

distribution loop shall be connected to the top of tank with spray ball provided inside the tank. The pipelines shall be designed at a velocity of minimum 1.2 m/sec in the return loop. The slopes shall be designed for greater than 1: 100.

UV purifier

UV purifier is installed at the supply line of the distribution loop for microbial disinfections. UV purifier is provided with an intensity monitor, which will sense the intensity of the UV lamps and gives out signal when intensity of lamp is low

Distribution system

- Centrifugal pump
- Interconnecting piping, Instruments and diaphragm valves for various applications (i.e. Sampling, Controlling, and Isolation)
- Sanitary Diaphragm Valves
- High Intensity Ultra Violet Unit
- Pressure indicators.
- Temperature Indicator cum Controller in return line
- Conductivity Sensor with FDV.
- Flow transmitter in return line
- TOC Analyzer

Control system and Instrumentation

Control system

The control panel shall consist of following

- Programmable Logic Controller [PLC]
- Human-machine interface (HMI) for operator controls
- Pneumatic controls (panel mounted)

- **The Programmable Logic Controller (PLC)**

- Versatile modular processor with power supply & memory back-up
- Digital input & digital relay output module
- RTD module
- Electrical safety / protection
- Equipment / interlocking for fail-safe operations via field devices water parameters monitoring and controls in normal mode of operation.
- Processing of set-point limit, alarms and time-based operations.
- The start-up and shutdown operations require intervention.

- **Human-Machine Interface (HMI)**

It is mounted on the panel-facial. Operator control is for on-line monitoring and Control of the process through different customized screens with direct access via predefined function keys on the operator console.

Instruments

The product water quality is measured online to confirm and control the purified water quality, the following parameters are monitoring in this system.

Following critical parameters are monitored at the different points in the system:

- pH
- Conductivity
- Pressure
- ORP
- Temperature
- Flow rate
- TOC Analyzer

Most of the possible risk concerning the handling/ operation of the Purified Water Generation, Storage & Distribution System has been considered in this RA document.

5 Participants

Name	Designation/ Department	Signature/ Date

6 Risk Management Process

A typical Risk management process consists of following steps:

- Risk Assessment:
  - Risk Identification
  - Risk Analysis
  - Risk Evaluation

- Risk Control
  - Risk Reduction
  - Risk Acceptance

- Result of Risk management processes
- Risk Review

- Risk Assessment consists of the identification of hazards and the analysis and evaluation of risks associated with exposure to those hazards.
  Risk identification is a systematic use of information to identify hazards referring to the risk question or problem description.

Risk analysis is the estimation of the risk associated with the identified hazards. It is the qualitative or quantitative process of linking the likelihood of occurrence and severity of harm.

Risk evaluation compares the identified and analyzed risk against given risk criteria. Risk evaluation considers the strength of evidence for all three of the fundamental questions.
The output of a risk assessment is either a quantitative estimate of risk or a qualitative description of range of risk. In case of qualitative description the risk is expressed using descriptors such as “high”, “medium” or “low”.

- Risk control includes decision making to reduce and/or accept risks. The purpose of risk control is to reduce the risk to an acceptable level. The amount of effort used of risk control should be proportional to the significance of the risk.
  Risk reduction focuses on processes for mitigation or avoidance of quality risk when it exceeds a specified (acceptable) level. Risk reduction might include actions taken to mitigate the severity and probability of harm.
  Risk acceptance is a decision to accept risk. Risk acceptance can be a formal decision to accept the residual risk or it can be a passive decision in which residual risks are not specified.
- The output/ result of the quality risk management process should be appropriately communicated and documented.
- Risk management should be an ongoing part of the quality management process. A mechanism to review or monitor events should be implemented.
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This document applies the risk management principles to identify the risks associated with the design, Construction and operational features of the proposed sterile formulation facility.
The objectives of this risk assessment are to:
• Review the design around a structured methodology
• Identify the failure modes and associated risks
• Check if the proposed control measures are adequate
• Identify recommendations to obtain a more acceptable risk level if required

6.1 Identifying GMP risk

Identification of Risk associated with the equipment, is generally based on prior experience and the concerns of the participants of risk assessment document.

The risks identified are categorized as “GMP risk” or “Non-GMP risk”.

GMP is defined as “the practices which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the marketing authorization.”

Thus, GMP covers all aspects of the manufacturing process: defined manufacturing process; validated critical manufacturing steps; suitable premises, storage, transport; qualified and trained production and quality control personnel; adequate laboratory facilities; approved

written procedures and instructions; records to show all steps of defined procedures have been taken; full traceability of a product through batch records and distribution records; and systems for recall and investigation of complaints.

Thus those risks which might have a direct or indirect impact on the quality of the product are classified as “GMP risk”. Also, those risks which might result in regulatory guidelines non-compliance are also classified as “GMP risk”.
For example: The Hygiene level of the manufacturing areas has a direct impact on the quality of the Product. Thus, it is classified as GMP risk.
The “Non GMP” risks include risks related to EHS, operational and other non-critical hazards.

Following types of risks are mainly identified during risk assessment process:

- Risk related to hygiene level of the manufacturing and supporting areas.
- Risks related to appropriate utilities and their control (eg. power source, compressed air etc.).
- Risks related to calibration/ preventive maintenance.
- Risks related to protection of the environment and health & safety of personnel.
- Risks related to cleaning & sterilization.
- Risks related to unidirectional flow of the material.
- Risks related to cross contamination of the products.
- Risks related to entry and exit of personnel and material.
- Risks related to all the environment features of the manufacturing areas.
- Risks related to requirement of particular rooms for different activities.
- Risks related to environment health and safety of personnel.

6.2 RISK ANALYSIS & EVALUATION

The risk analysis is performed using a qualitative basis of approach.

Qualitative analysis uses word form or descriptive scales to describe the magnitude of potential consequences/ impact and the likelihood that those consequences will occur.

The qualitative measures of likelihood includes descriptors like “Unlikely”, “Possible” and “Likely”, whereas the qualitative measures of consequence/ impact includes descriptors like “Minor”, “Moderate” and “Major”.

Qualitative measures of likelihood

Level	Descriptor	Example detail description
1	Unlikely	May occur at some time
2	Possible	Might occur at some time
3	Likely	Will probably occur in most circumstances

Qualitative measures of consequence/ impact

Level	Descriptor	Example detail description
1	Minor	• No impact on the product quality or outcome of the equipment. • Features required for easing equipment operation.
2	Moderate	• No direct impact on product quality/ outcome of equipment. However may indirectly affect the product quality. • Minor effect on personnel health • Used in the initial stage of operation, however it may affect the final output but those are not used for final release of output. • Effect on environment such as clean room.
3	Major	• Features having direct impact on product quality/ outcome of equipment like contact parts MOC, Surface finish, Control system, Process air quality etc. • Failure could lead to regulatory non-compliance. • Loss/ damage to equipment or its critical sub-components • Critical instruments not calibrated or not of desired range or accuracy. • Proper supporting documentation not provided. • Major effect on personnel health

Based on the above parameters of likelihood and consequence a qualitative risk analysis matrix is prepared to identify the overall Level of Risk, as mentioned in table below.

Qualitative risk analysis matrix – level of risk

Likelihood	Consequences/ Impact		
	1 – Minor	2 – Moderate	3 – Major
1 (Unlikely)	Low	Medium	High
2 (Possible)	Low	Medium	High
3 (Likely)	Medium	High	High

The final Risk level shall thus be described using descriptors such as “Low”, “Medium” & “High”, where each descriptor implies the following meaning:

Low – Risk can be accepted or ignored. These do not affect the final quality of the equipment/ system and it can be managed by routine procedures and are unlikely to need specific application of resources.

Medium – Risk required ongoing monitoring and review, to ensure level of risk does not increase. Otherwise managed by routine procedures.

High – Action plans must be developed, with clear assignments of individual responsibilities and timeframes.

7 Risk Assessment

In the following section a table is produced for the risk assessment. The significance or instruction for each column is described in the following paragraph.

Column 1 : **Serial number** of the Risk assessment item

Column 2 : **Process step/Component**: Identify the process step or component associated with the risk.

Column 3 : **Risks:** Identify the type of risk associated with the process or component

Column 4 : Verify that whether risk have **GMP impact** in terms of Yes/ No.

Column 5 : **Justification:** Provide justification for declaring both Yes/No for GMP impact in column 4.

Column 6 : For the risk **other than of GMP impact**, write that what is/are the type of risks e.g. EHS, operational, etc.

Column 7 : **Justification:** Provide justification for considering the risk.

Column 8 : **Risk level:** Determine the risk level as High, Medium or low based on the impact.

Column 9 : **Risk Control:** It is further divided into the following three sections:

Column 9a : **Mitigation Method:** Write the risk mitigation strategy as considered in the design.

Column 9b : **Residual risk level:** After the risk mitigation what is the residual risk level, whether it is Acceptable, Low or Medium.

Column 9c : **Test document:** Write the test point where the risk mitigation strategy will be verified.

Column 10 : **Status of RA:** Mention the status of the Risk assessment point i.e. whether it is ‘Closed” or “Open”, after the execution/ approval of the Test document.

RISK ASSESSMENT FOR PURIFIED WATER GENERATION, STORAGE AND DISTRIBUTION SYSTEM

S. No. (1)	Process steps/ component (2)	Risk (3)	GMP Risk Yes/ No (4)	Justification (5)	Other Risk type (6)	Justification (7)	Risk Level (8)	Risk Control (9)			Status of RA (10)
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PRETREATMENT SYSTEM											
1.	Bore well water (Raw water)	The quality of the bore water is not good it has high TDS and silica content.	Yes	The final desired water quality will not be attained.	No	NA	High	• Ultra filtration followed by Industrial R.O to be considered before the final R.O. • MGF shall be considered in design to filter & remove suspended impurities from bore well water. • After MGF water will be transferred to potable water storage tank. • Raw water testing shall be done before the design of the system.	Acceptable	IQ	
2.	Bore well water (Raw water)	Increased microbial and particle contamination of the infeed raw water	Yes	The system shall be inefficient to remove the increased microbial and particulate contamination.	Operational	Frequent changes of the RO membrane	Low	• The raw water from the bore well shall be transferred to a closed underground raw water storage tank. • Bore well water discharge line shall be provided with the facility for adding sodium hypochlorite solution on line to raw water.	Acceptable	IQ & OQ	
3.	Bore well water (Raw water)	Water cannot be withdrawn completely from the storage tank	Yes	This is required during cleaning of the tank or when tank is contaminated chemically or microbiologically.	No	NA	Low	Tank bottom shall be sloped to a small sump from where water can be pumped out.	Acceptable	IQ & OQ	
4.	Bore well water (Raw water)	Tank is directly exposed to environment	Yes	This may lead to increased microbial and particulate contamination	Operational	Cleaning of the tank will be difficult.	Medium	The tank shall be properly closed with lid	Acceptable	IQ	
5.	Bore well water (Raw water)	Cleaning of the underground storage tank is not possible.	Yes	After a long period of time the microbial and particulate contamination may be increased and the system may be inefficient to remove the increased microbial and particulate contamination.	No	NA	Low	• The tank shall be provided with man entry for cleaning in regular interval. • The SOP for cleaning shall be prepared and the frequency of the cleaning shall be established.	Acceptable	IQ & OQ	

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6.	Bore well water (Raw water)	Insufficient quantity of raw water.	No	The quantity of raw water shall not have any impact on the product quality.	Operational	The process may stop due to lack of raw water.	Low	• The raw water storage tank shall be sized as per the downstream requirements. • The tank shall be provide with level switch for high and low level to have a uninterrupted flow.	Acceptable	IQ & OQ	
7.	Bore well water (Raw water)	Tank wall and floor is not leak proof	Yes	Unexpected intrusion of micro-organism	EHS	Water may be contaminated by sewage water or contaminated by heavy minerals.	High	• RCC Injection grouting should be recommended inside the tank. • In regular basis tank should be inspected for any cracks.	Low	IQ	
8.	Bore well water (Raw water)	Sampling of the bore well water is not possible	Yes	The bore water quality shall decide the final purified water quality and the extent of the pre-treatment.	No	NA	High	• Sampling point to be provided for sampling of bore well water. • Considering the bore well water quality the pre-treatment process shall be established.	Acceptable	IQ	
9.	Bore well water (Raw water)	Overflow of raw water in underground storage tank.	No	Over flow water shall not affect the product quality	Operational	• Spillage of excess water requires frequent cleaning of the area. • Loss of resources i.e. water	Low	The ground water storage tank shall be provided with level indicator for high water level in the tank.	Acceptable	IQ	

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10.	Bore well water (Raw water)	Water stagnant in underground tank.	yes	The water stagnant will rise the microbial content in the water	No	NA	High	• An online sodium hypochlorite dosing in water is considered in the storage tank with sampling points. • During validation sanitization process and frequency is to be established. SOP should be written, confirmed and implemented.	Acceptable	IQ & OQ	
11.	Sodium hypochlorite level	Low chemical level in dosing tank	Yes	Low level of chemical will not disinfect the water as per the requirement	No	NA	High	• The dosing tank shall be provided with level indicator for monitoring of high and low level of chemical. • Alarm shall be provided in case of low level of sodium hypochlorite in dosing tank.	Acceptable	IQ & OQ	
12.	Water filtration	Contamination of the RO unit with the coarse suspended particles in the raw water.	No	The coarse particles shall be removed in the RO and hence no impact on the product quality	Operational	The RO unit shall be choked and damaged by the coarse particle	Low	Multi grade filter shall be provided for the filtration of coarse particles.	Acceptable	IQ	
13.	Multi Grade Filter	Choking of the MGF	No	Choking of the MGF shall have no impact on the product quality	Operational	Frequent removal of the filters	Low	• Multi grade filter shall be dismountable type for easy removal and installation. • Installing of Pressure indicators at the inlet of MGF and across the filter to detect the choke. • Sampling valve shall be provide at inlet and outlet. • Backwash with high flow rate. • Operating, Preventive Maintenance SOP & Training.	Acceptable	IQ & OQ	

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14.	Multi Grade Filter	Material of construction is not compatible with water in long run as the water has chlorine content.	No	NA	Operational	Iron and rust particles may carry over with water and increases the load on the down stream equipment. Life time of the equipment will come down.	Low	• The Multigrade filter MOC to be well designed. • Fiber reinforced plastic (FRP) is recommended.	Acceptable	IQ	
15.	Multi Grade Filter	Required water velocity is not available to pass through the filter.	No	NA	Operational	Reduction in the velocity of water will affect in the total output of the water system. Backwash with high flow rate is not possible.	Medium	• Transfer pump before MGF should be of suitable capacity. • Installing of Pressure indicators at the inlet of MGF and across the filter to detect the water velocity continuously.	Acceptable	IQ	
16.	Multi Grade Filter	As the porosity of the MGF is high only the coarse particle will be withhold	No	NA	Operational	The tiny particle may pass through and choke the R.O membrane.	Medium	10 Micron cartridge filter can be considered to address the same in the downstream.	Acceptable	IQ	
17.	Multi Grade Filter	Microbial growth in MGF	Yes	During non operation of the system the water hold up will be stagnant and possibility for microbial growth.	No	NA	Medium	• Filter will be designed to be complete drainable type to avoid such hold up and installation of pressure gauges. • As the water is chlorinated the possibility of microbial growth is considerable less.	Acceptable	IQ & OQ	

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18.	Water Softening	Reduction in efficiency of the RO unit due to hardness in the raw water.	No	The hardness of the raw water shall be removed in the RO and hence no impact on the product quality	Operational	The RO membrane shall need to be replaced frequently.	Low	Softener system shall be provided for the reducing the hardness of water.	Acceptable	IQ	
19.	Softener	Regeneration of Softener not possible	No	The hardness of the raw water shall be removed in the RO and hence no impact on the product quality.	Operational	The efficiency of RO unit would be reduced.	Low	Softener shall be provided with a brine measuring tank and a regeneration system along with rinsing.	Acceptable	IQ	
20.	Softener	Softener having low OBR	No	No effect on the final quality of water.	Operational	Softener would have to be regenerated frequently.	Low	The OBR of the softener should be sufficient so as to allow 8 hours of continuous operation.	Acceptable	OQ	
21.	Softener	Microbial growth in resin	Yes	During non operation of the system the water hold up will be stagnant and possibility for microbial growth.	No	NA	Medium	Whole installation shall be designed as complete drainable type to avoid such hold up and installation of pressure Gauges at the inlet & outlet is recommended.	Acceptable	IQ & OQ	
22.	Softener	Material of construction is not compatible with water in long run.	No	NA	Operational	Mineral particles may carry over with water and increase the load on the downstream equipment. Life	Low	• The Softener MOC to be well designed. • Fiber reinforced plastic (FRP) is recommended	Acceptable	IQ	

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						time of the equipment will come down.					
23.	Filtration	The raw water has high slit density index	Yes	Feed water to RO shall have high slit density index	Operational	The RO unit shall be choked and damaged	High	Ultra filtration shall be provided before RO to reduce the slit density index	Acceptable	IQ	
24.	Ultra-Filtration unit.	Choking of filter may happen due to sludge particles in the raw water.	Yes	Effective output is not attainable.	Operational	Increase the load on the pump and operational delay and there by the down stream flow requirement is not achievable.	High	• Installing of Pressure indicators at the inlet of the filter and across the filter to detect the choke. • Auto Backwash with high flow rate at regular intervals. • Operating, Check Maintenance SOP & Training.	Acceptable	IQ, OQ & SOP	
25.	Ultra-Filtration unit.	Microbial growth in filters.	Yes	During non operation of the system the water hold up will be stagnant and possibility for microbial growth.	Yes	Membrane may clog	Medium	• Whole installation shall be designed as complete drainable type to avoid such hold up and installation of pressure Gauges at the inlet & outlet is recommended. • System to be designed with sanitization facility. • Backwashing shall be done.	Acceptable	IQ & OQ	

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26.	Water collection tank (After Ultra filtration)	• Ultra-filtered water storage tank MOC is not compatible. • Tank cannot be cleaned properly.	No	NA	Operational	Iron and rust particles carry over with water increase the load on the down stream equipment. Life time of the equipment will come down.	Low	• Tank to be designed with compatible media to with stand the property of the water. (HDPE/SS304 Recommended) with level switch and sampling points. • Proper cleaning method and interval will be defined in the SOP. • Provision for Hot water sanitization should be available.	Acceptable	IQ & OQ	
27.	First pass RO	• Not provided. • Sampling after RO is not possible	Yes	• RO unit is required to generate process water required for purified water generation system. • Water quality shall not be checked	No	NA	High	• RO unit shall be provided as a part of pre treatment unit, where water is separated from dissolved salts in solution by filtering through a semi permeable membrane. • Sampling point shall be provided after RO.	Acceptable	IQ	
28.	Feed Pump for Reverse Osmosis	Water flow rate is not sufficient.	No	NA	Operational	• If sufficient water flow is not available cavitation of the pump takes place. • Pump can't deliver the required pressure of R.O system.	Medium	• System should be designed in such a way that the ultra filtered water to be collected in a UF storage tank with level indicator and controller to give an undisturbed continuous flow to the R.O. feed pump. • Low pressure switch shall be provided at the inlet of RO feed pump. • Alarm to be provided in case of low pressure.	Acceptable	IQ & OQ	
29.	First pass RO	Various process parameter like conductivity and flow rate are not monitored	Yes	Critical GMP process parameter	No	NA	High	• The RO unit shall be provided with the provision for monitoring, indicating and controlling the conductivity and flow rate of water. If the output water is not meeting the desired result the water will be drained without going to the downstream system. • Alarm to be provisioned in case of high conductivity & low/ high feed to RO.	Acceptable	IQ & OQ	

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30.	First pass RO	Possibility of microbial growth in the industrial R.O	Yes	Purified water quality will be affected.	No	NA	High	• The R.O shall be hot water & chemically sanitizable, and the system shall be provide with CIP system to clean and sanitize the R.O. • SOP for sanitization and interval for sanitization shall be adopted during validation.	Acceptable	IQ, OQ & SOP	
31.	SMBS dosing not provided before RO unit	Chlorine content is high	Yes	The chlorine content in water shall lead to oxidation of the RO membrane and hence shall affect the final water quality.	Operational	The membrane shall need to be replaced frequently.	High	• The dosing unit shall be provided for sodium meta bisulfite (SMBS) addition to the water before RO unit. • The ORP sensor shall be provided for monitoring the chlorine content of water with auto dump valve.	Acceptable	IQ & OQ	
32.	SMBS level	Low chemical level in SMBS dosing tank	Yes	Low level of chemical will not release SMBS as per requirement to neutralize chlorine in water.	No	NA	High	• The dosing tank shall be provided with level indicator for monitoring of high and low level of SMBS. • Alarm to be provisioned in case of low level.	Acceptable	IQ & OQ	
33.	Antiscalant dosing	Not provided	No	NA	Operational	Precipitation of silica on RO membrane can damage the membrane	Low	Antiscalant dosing shall be provided before RO	Acceptable	IQ	

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34.	Antiscalant level	Low chemical level in antiscalant dosing tank	Yes	Low level of chemical will not release antiscalant as per requirement.	Operational	Precipitation of silica on RO membrane may increase.	High	• The dosing tank shall be provided with level indicator for monitoring of high and low level of antiscalant • Alarm to be provisioned in case of low level.	Acceptable	IQ & OQ	
35.	pH correction dosing system	pH dosing not provided	No	Recommended pH of water not maintained.	Operational	In high and low pH the minerals in the water will be in saturation form and tends to set over the R.O membrane.	Medium	As the saturation of the minerals decreases in the neutral pH(i.e.) at 7.5 - 8.5, a pH correction dosing system can be provided to correct the pH to required level to have a better control over filtration.	Acceptable	IQ	
36.	pH correction dosing chemical level	Low chemical level in pH correction dosing tank	Yes	Low level of chemical will lead to improper maintenance of pH of the feed water to RO leading to decrease in efficiency of RO.	No	NA	High	• Level sensor shall be provided in case of low level of chemical in pH correction dosing tank. • Alarm to be provisioned in case of low level.	Acceptable	IQ & OQ	
37.	Chemical dosing	Wrong Weighing of chemicals for dosing	Yes	Deviation chemical composition not as requirement	No	NA	High	Operating SOP for weighing the chemical composition.	Low	SOP	

FINAL TREATMENT

RISK ASSESSMENT FOR PURIFIED WATER GENERATION, STORAGE AND DISTRIBUTION SYSTEM

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								Mitigation Method (9a)	Residual risk level (9b)	Test Document (9c)	
38.	EDI unit	Not Provided	Yes	Purified water quality will not be attained.	No	NA	High	EDI shall be provided after RO membrane so as to reduce the conductivity of water so as to meet regulatory standards.	Acceptable	IQ	
39.	Second pass RO unit	Water quality fails at outlet of RO-+EDI unit.	Yes	Water quality must meet the specified conductivity.	No	NA	High	• Water of failed quality after RO unit shall be auto dumped through dumping valve. • Water of failed quality after EDI shall be recirculated back to recovery tank.	Acceptable	IQ & OQ	
40.	RO+EDI unit	The operation is not auto controlled	Yes	The water quality may be affected by manual operation of the RO unit due to human errors.	Operational	The manual operation is difficult.	High	The RO unit shall be fully automatic and PLC based.	Acceptable	OQ	
41.	RO+EDI unit	• Various process parameter like pH, conductivity, flow rate, TOC are not monitored. • Sampling point after EDI not provided	Yes	• Critical GMP process parameter. • Water quality could not be checked	No	NA	High	• The unit shall be provided with the provision for monitoring, indicating and controlling the, conductivity, TOC and flow rate of water. • Sampling point after EDI shall be provided	Acceptable	IQ & OQ	

RISK ASSESSMENT FOR PURIFIED WATER GENERATION, STORAGE AND DISTRIBUTION SYSTEM

S. No. (1)	Process steps/ component (2)	Risk (3)	GMP Risk Yes/ No (4)	Justification (5)	Other Risk type (6)	Justification (7)	Risk Level (8)	Risk Control (9)			Status of RA (10)
								Mitigation Method (9a)	Residual risk level (9b)	Test Document (9c)	
42.	RO + EDI Unit	Possibility of microbial growth in the R.O + EDI unit	Yes	Purified water quality will be affected.	No	NA	High	• The R.O + EDI Unit shall be hot water sanitizable. • SOP for sanitization and interval for sanitization shall be adopted during validation.	Acceptable	IQ, OQ & SOP	
STORAGE AND DISTRIBUTION OF PURIFIED WATER											
43.	Storage of purified water	No storage of purified water before use.	No	The water quality shall not be affected if not stored.	Operational	It is difficult for providing several user points from the single point of generation	Low	• The purified water generated shall be stored in a storage tank. • The purified water from the storage tank shall be distributed to the user points through distribution loop and returned back to PW storage tank	Acceptable	IQ & OQ	
44.	PW Storage Tank	Low water level in the storage tank.	No	The water level shall not affect the water quality	Operational	• No water in the tank, the Pump will run dry. • It may lead to damage the pump and affect the process. • Manual observation of the water level is difficult	Low	• The PW storage tank shall be provided with level switch for monitoring of low water level. • PW Distribution pump should turn off in case of low level PW in storage tank. • Alarm to be provisioned in case of low level.	Acceptable	IQ & OQ	
45.	PW Storage Tank	Overflow of Purified water from storage tank.	No	Over flow water shall not affect the water quality	Operational	• Overflow of excess water requires frequent cleaning of the area. • Loss of resources in form of Purified water.	Low	• The Purified water storage tank shall be provided with level switch for monitoring of high water level. • The flow to the tank shall be stopped if tank is full and the water shall be re-circulated back to UF water storage tank. • Alarm to be provisioned in case of low level.	Acceptable	IQ & OQ	

RISK ASSESSMENT FOR PURIFIED WATER GENERATION, STORAGE AND DISTRIBUTION SYSTEM

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								Mitigation Method (9a)	Residual risk level (9b)	Test Document (9c)	
46.	PW Storage Tank	Water stagnant in the purified water collection tank.	Yes	Possibility of Microbial growth.	No	NA	High	Spray balls will be considered at the return flow to create proper agitation.	Acceptable	IQ	
47.	PW Storage Tank	Water could not be drained.	Yes	During sanitization of PW tank or in case of contamination the water needs to be drained.	No	NA	High	• The storage tank should be designed as complete drainable type to avoid hold up. • A manual drain valve shall be provided for draining of the water from the tank.	Acceptable	IQ	
48.	Storage tank Temperature	Control of tank temperature is not provided.		Temperature is key parameter for hot water sanitization	No	NA	Medium	Temperature indicator cum controller shall be provided for monitoring of storage tank temperature.	Acceptable	IQ	
49.	PW Storage Tank	Vent filter not provided	Yes	Possibility of environmental contamination of PW.	Safety	Pressure might be developed inside the storage tank	High	Storage tank should be provided with hydrophobic type of vent filter with SS housing.	Acceptable	IQ	
50.	Vent Filter	Vent filter is not heated.	Yes	Water droplets may condense and remain on the surface of vent filter during sanitization of the Storage tank, due to difference in temperatures. May lead to microbial contamination.	No	NA	High	• Vent filter should be provided with an electrically heated housing so as to heat and maintain the filter temperature during sanitization process. • Temperature sensor to be installed on the vent filter housing to monitor the temperature of vent filter.	Acceptable	IQ & OQ	

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								Mitigation Method (9a)	Residual risk level (9b)	Test Document (9c)	
51.	Vent Filter	Filter integrity not possible	Yes	Testing of filter not attained , risk of contamination	No	NA	High	• Filter housing should be equipped with ports for integrity test. • Filter integrity test at regular intervals. • Regular exchange of filter cartridges (exchange in controlled area) • SOP's: Filter tests; Maintenance	Acceptable	IQ, OQ & SOP	
52.	Vent Filter	Affected by the high temp. during the sanitization process	Yes	Filter efficiency will decrease leading to further contamination of the PW.	No	NA	High	• High temp. resistant filters should be used. • Provision shall be incorporated in the SOP "Preventive maintenance" to check the efficiency of the filters.	Acceptable	IQ & SOP	
DISCHARGING OF OUTPUT											
53.	Distribution	• Water stagnancy in the distribution line to different user points. • No sampling point provided.	Yes	• Water contamination may increase due to the bio-load in the distribution line to different user points. • Sampling point is required to check water quality in loop and user points	Operational	Removal of stagnant water each time before use shall be very difficult.	High	• The water distribution shall be in a loop system. The water shall be in continuous flow in the loop. • All pipelines shall have drainable slope of > 1:100. • Discharge pump should b self-draining type. • The dead leg in the loop shall not be more than 1.5d. (d- diameter of the extended part) • Zero dead leg type sampling points shall be provided at return loop and all user points.	Acceptable	IQ	

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54.	Distribution	Flow rate in the loop is low.	Yes	Low flow rate tends to bio-film formation in the pipe.	No	NA	High	• Specified flow rate (>1.2 m/s) will be maintained in the loop at return line. • Flow switch/sensor will be considered on the return line with VFD connection to the distribution pump. • Alarm shall be generated in case of flow rate decreased from 1.2 m/s.	Acceptable	IQ & OQ	
55.	Distribution	Distribution loop is not provided with UV purifier	Yes	Water contamination may occur	No	NA	Medium	UV purifier shall be provided in the distribution loop with intensity meter for the UV lamp	Acceptable	IQ & OQ	
56.	Distribution	High conductivity in return line	Yes	High conductivity water may contaminate the fresh Purified water	No	NA	High	• Conductivity sensor shall be provided in the return line with auto-dumping facility in case of high conductivity. • Alarm provision in case of high conductivity.	Acceptable	IQ & OQ	
57.	Distribution	High TOC	Yes	Performance failure	No	NA	High	• Online TOC analyzer to be installed at return line to tank. • Provide auto-dumping valve coupled with TOC analyzer. • Alarm provision.	Acceptable	IQ & OQ	
58.	PW Storage tank & Distribution System	Sanitization not possible	Yes	Possibility of microbial growth	No	NA	High	• A suitable Sanitization process shall be provided in the PLC for effective sanitization of the PW storage tank and distribution system. • Tank should be jacketed and should be plant steam supply for heating of water during sanitization. • Temperature sensor shall be provided in the PW storage tank and on return line to monitor temperature during sanitization. • Tank jacket shall be insulated to prevent loss of heat during sanitization.	Acceptable	IQ & OQ	

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								• Alarm to be provisioned in case of High/ low temp. during sanitization.			
Equipment Construction											
Internal Surface											
59.	Surface	Internal surface/ contact parts is not compatible with the water	Yes	May lead to the water contamination	No	NA	High	• Pre-treatment stage - all interconnecting pipes, dosing tanks, sampling valves shall be UPVC or SS 304 and the storage tanks shall be of HDPE. • After second pass RO - Metallic critical contact parts (piping, PW storage tank) as well as instruments, level sensors, valves etc, shall be of SS 316 or better. Pipelines should be electro polished & orbitally welded. • Supporting structure shall be of SS 304 or better. • Diaphragm Valves: SS 316L, electro polished. • Purified water distribution pipeline shall be of SS 316 or better.	Acceptable	IQ	

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60.	Polymeric materials	Polymeric materials are not compatible and are not replaceable	Yes	Shall lead to water contamination	No	NA	High	• Gaskets (shall be high temperature & pressure resistant) and O-rings coming in direct / indirect contact surfaces shall be made up of food grade polymeric materials only and shall be hat resistant. • The easy change of gaskets must be possible. • Vendor shall provide the certificate for food grade polymeric material.	Acceptable	IQ	
61.	Welding Joints	Weld joints not ground properly and are not passivated	Yes	Uneven and improperly ground weld joints will form a space for dust accumulation	No	Na	High	All welds shall be ground finished to < 1.2 µm Ra and properly passivated and orbital welding should be done.	Acceptable	IQ	
62.	Finishing	Internal finish is not proper	Yes	May lead to improper cleaning of the surface which will lead to microbial growth hence product contamination	No	Na	High	All internal metallic surface shall be mirror polished with ≤ 0.5µm Ra	Acceptable	IQ	
63.	Joints	Joints are leaking	Yes	Water contamination may affect the final water quality.	No	NA	High	• Suitable gaskets shall be provided for air tight connection which shall be replaceable. • Quick release Triclover joints are recommended.	Acceptable	IQ	
External Surface											

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64.	Surface	Surface is not clean room suitable	Yes	May lead to the clean room contamination	No	NA	Medium	Supporting structures and frames shall be SS 304.	Acceptable	IQ	
65.	Finishing	External finish is not proper	Yes	May lead to the microbial growth	No	NA	Medium	External surface shall be free from sharp edges, corners, crevices etc., all metallic external surface shall be matt finished	Acceptable	IQ	
66.	Lubricant	Lubricant used is not food grade and is toxic in nature	Yes	Used lubricants coming in contact of the potential product contact surfaces may lead to the contamination of the product	No	NA	Medium	Lubricant shall not enter in processing zone of equipment. Any lubricant, if used in the equipment must be food grade and non-toxic. Vendor shall provide the certificate	Acceptable	IQ	
PLC/Control System											
67.	Process automation	Process parameters are not controlled automatically.	Yes	Possibility of human error leads to a process which is not validated	No	Na	High	• The equipment shall control & detect failure mode automatically. • The System shall be PLC based and fully automatic.	Acceptable	IQ & OQ	
68.	Man-machine Interface	Process / process status not visible for operating personnel.	Yes	Operating personnel must have knowledge on the process status	No	NA	High	MMI shall be provided with adequate display and clean room suitable key board/Touch screen for operation.	Acceptable	IQ	
69.	Man-machine Interface	Display language not identified.	Yes	Pre-requisite for the GMP compliant operation	No	NA	High	The language on the display of MMI should be English language only.	Acceptable	OQ	

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70.	Man-machine Interface	Recorder failure	Yes	Basis GMP requirement (incomplete / no documentation)	No	NA	High	• Data backup for process data must be foreseen (electronic recording, 21 CFR part 11 compliant). • Diagnostic function test to be a part of qualification activity.	Acceptable	IQ/ OQ	
71.	Man-machine Interface	Monitoring/recording and documentation of GMP relevant data not possible	Yes	Basic GMP requirement	No	NA	High	• It should be possible to monitor/record GMP relevant data (e.g. recorder with compliance to GAMP 5 / 21 CFR, Part 11 etc.) • Batch records / print outs to be defined. • Printout facility should be available with fade proof prints.	Acceptable	OQ	
72.	Control system	Control system does not detect failures and generate alarms	Yes	Process optimization and validation is not possible	No	NA	High	Failure of set parameters gets indicated as alarms and machine stops.	Acceptable	OQ	
73.	PLC / Control system	Power failure / emergency stop	Yes	Process out of specification	EHS	May lead to some accident	High	• Operator settings unchanged and restored after emergency stop / power failure; • Alarm message; • Machine must not start automatically without operator intervention after incident • SOP for 'Maintenance and operation of PW Generation, Storage & Distribution System'.	Acceptable	OQ	
74.	PLC / Control system	Status parameters not clear	Yes	Process for the particular product at particular stage can't be regulated easily.	No	NA	High	• Status parameters should remain displayed at each process stage. • The flow of the process shall be provided with the help of arrows. • Alarm should also be visualized along with the fault displayed.	Acceptable	OQ	

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75.	PLC / Control system	Malfunction	Yes	Correct function basic requirement for GMP-compliant operation	No	NA	High	• Supplier analysis (quality management system for software and control system hardware development) • Input/ Output test implementation in qualification activities • The system must contain all necessary protection devices to ensure that the equipment and article remain in safe condition.	Acceptable	OQ	
76.	Accessibility to PLC	Parameter settings not identified universally	Yes	Basic GMP requirement	No	NA	High	Parameters settings should be in numeric only.	Acceptable	OQ	
77.	PLC / Control system	Time measurement works incorrect	Yes	Process insufficient	No	NA	High	• PLC Clock verification • SOP “calibration and maintenance” • Time synchronisation of system	Acceptable	OQ & SOP	
78.	PLC / Control system	No protection of PLC against manipulation & changes.	Yes	Basic GMP requirement.	No	NA	High	Minimum 3 level password protections should be provided. ➢ Level 1: for operator settable parameters. ➢ Level 2: for editing cycle parameters. ➢ Level 3: for admin/ engineering level setting.	Acceptable	OQ	

Measuring Instruments

RISK ASSESSMENT FOR PURIFIED WATER GENERATION, STORAGE AND DISTRIBUTION SYSTEM

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79.	Measuring instruments	Measuring instruments not suitable	Yes	Improper measurements	No	NA	High	• Measuring instruments must have a suitable measuring range. • Operational range of measuring instruments > instrument working range. • They must have appropriate accuracy.	Acceptable	IQ	
80.	GMP relevant measuring instruments	Measuring instruments cannot be dismounted	Yes	Defective instruments must be dismounted for exchange and calibration	No	NA	High	• Mounting of instruments must give the possibility for dismounting and replacement • Constructional solution: easy access for calibration activities shall be given	Acceptable	IQ	
81.	Measuring instruments	• Instruments not calibrated. • Re-calibration is not possible	Yes	Non calibrated instruments may lead to false machine functions	No	NA	High	• Measuring instruments should be calibrated, traceable to national or international standards. • Re-calibration of instruments should be possible.	Acceptable	IQ & OQ	
System Cleaning and sanitization											
82.	Cleaning	Cleaning is not possible	Yes	Cleaning is basic GMP requirement	No	NA	Medium	• The external surface shall be smooth for easy manual cleaning. • The storage tank and distribution system shall be hot water sanitizable.	Acceptable	IQ& OQ	

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83.	Sanitization	Sanitization not possible	Yes	Sanitization of the water system is basic process and GMP requirement	No	NA	Low	• First RO shall be chemical & Hot Water sanitizable. • The RO shall be hot water sanitizable. • The storage tank and distribution line shall be hot water sanitizable. • Separate CIP system provision to be provided for chemical sanitization.	Acceptable	IQ & OQ	
84.	Cleaning and sanitization automation	Cleaning and sanitization process parameters are not controlled automatically	Yes	Possibility of human error leads to a cleaning procedure which is not validated	No	NA	High	• Cleaning process shall be performed by a automatically controlled system. • Suitable PLC control shall be considered	Acceptable	IQ& OQ	
85.	Labelling	Labelling of components inappropriate	Yes	Prerequisite for qualification	No	NA	High	Unique identity no. / flow direction must be on components / media, operator panel, etc. (e.g. according to P&ID). Labels affixed on the equipment should be heat resistant. All labelling in English language and according to project standard.	Acceptable	IQ	
Maintenance											
86.	Maintenance	Malfunctions due to worn parts	Yes	Basic GMP requirement	No	NA	High	• Machine shall be easy to maintain. • Preventive maintenance procedure should be available • The unit must contain necessary protection devices to ensure that the equipment & the article remain in a safe condition.	Acceptable	IQ & SOP	

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87.	PW distribution system	Discharge Pump failure	No	Distribution system will be stopped and water may become stagnant leading to decrease in temperature and hence increase in bio burden.	Operational	Generation gets affected	Medium	• A standby pump should be provided. • Alarm provision in case of pump overload.	Acceptable	IQ & OQ	
System Safety											
88.	Electrical system	Electrical systems are not verified for safety	No	It will not affect the final quality of water.	EHS	May lead to an accident	Medium	All electrical systems shall be tested for safety and shall be provided with safety markings e.g. C.E. marking.	Acceptable	IQ	
89.	Noise level	Noise level liberated by the system is high.	No	It will not affect the final quality of water.	EHS	Heavy noise will cause problems to the service persons	Medium	The noise liberated by the system shall not be more than 80 db from 1m from the system.	Acceptable	OQ	
90.	Emergency stop	Instantaneous stopping of the equipment not possible	No	Does not have any impact on quality of the product	EHS	Emergency stop function is required for equipment, personnel and product protection	High	Emergency stop with alarm to be installed on accessible areas on PW generation as well as distribution system.	Acceptable	IQ & OQ	

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91.	Utility Failure	Compressed air is low		Improper function of pneumatic instruments leads to improper output.	Operational	May leads improper function of the system	High	• Compressed air pressure shall be indicative with alarm if low. • The total system shall be shut down if the compressed air is low.	Acceptable	IQ & OQ	
92.	Heating	Excess heating & Excess pressure	No	Does not have any impact on quality of the product.	EHS	Environmental & operator safety hazards.	Medium	▪ Temp. & Pressure limit for the resistance of the equipment should be defined & feeded. ▪ Elevated temp. & pressure should be alarmed leading to the opening of the safety valve.	Acceptable	IQ &OQ	
Documentation											
93.	User	Faulty operation & maintenance	Yes	SOPs are basic GMP-requirement	No	NA	High	• All end-users have to be trained on SOPs • Training of SOPs has to be documented • Training on the job of end users by vendor. • Training on operation, setting parameters, trouble shooting & maintenance related activities.	Acceptable	OQ & SOP	
94.	User	Operation SOP does not contain proper information and user may operate system	Yes	User may make a wrong decision.	No	NA	High	System operation SOP must be reviewed with all aspects and approved.	Acceptable	OQ	

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95.	User	Unauthorized person tries to start/stop the system	Yes	Untrained persons may damage the system or product quality may be affected	No	NA	High	• System should not start without password. • Key-switch should be provided for system power up. OR • Physical entry to equipment room is restricted.	Acceptable	IQ & OQ	
96.	Vendor Documentation	Technical documentation from vendor not adequate	Yes	Adequate technical documentation is basic GMP requirement for qualification and operation of the System	No	NA	Medium	Vendor documentation shall comprise: • Material certificates • Welding certificates along with welder qualification certificate. • Boroscopy reports • Slope Verification report • Pressure leak test report • Passivation report • Operating instruction • Maintenance instructions • Spare part lists • Drawings - P&I-diagrams - Electrical diagrams • Functional design specification • HMI functions with screen shot • List of failure indications	Acceptable	IQ	

8 Summary & Conclusion

- The Risk Assessment was performed to establish the design parameters of the equipment so as to meet the desired performance of the equipment i.e. Purified Water Generation, Storage & Distribution System.
- The critical risks pertained to GMP and other than GMP, were analyzed with justification and mitigation procedures.
- For each recognized GMP-risk and other than GMP risks, necessary measures are defined. Organizational measures, like SOPs, are also possible measures for special GMP-risks. The availability of these SOPs will be checked during the performance of the OQ.
- The risks where conceptual procedures shall be employed, standard operating procedures (SOPs), Preventive maintenance schedules, Certificates and related documents indicated as mitigation procedures shall be ensured at respective test points

*"It is concluded that the **Risk Assessment** performed for the equipment will prevent the risk of failures of critical parameters during, design commissioning, installation, operation and performance of the equipment".*

9 Abbreviations

EU-GMP	:	European – Good Manufacturing Practice
EHS	:	Environment Health Safety
PID	:	Proportional Integral Derivative
GMP	:	Good Manufacturing Practice
ICH	:	International committee for harmonization
PTFE	:	Polytetrafluoroethylene
RA	:	Risk Assessment
NMT	:	Not More Than
SOP	:	Standard Operating Procedure
SS	:	Stainless Steel
Ra	:	Roughness Average
P&ID	:	Process/ Piping & Instrumentation Diagram
PLC	:	Programmable Logic Controller
MMI	:	Man Machine Interface
CFR	:	Code of Federal Regulations
UPS	:	Uninterrupted Power Supply
CE	:	Conformité Européene
db	:	Decibel
IQ	:	Installation Qualification
OQ	:	Operational Qualification
PQ	:	Performance Qualification
O&M	:	Operation and Maintenance
GA	:	General Arrangement
USP	:	United States Pharmacopeia
IPSI	:	Integrated Project Services International, New Delhi
SMBS	:	Sodium Meta bi Suphite
ORP	:	Oxidase Reduction Potential
RO	:	Reverse Osmosis
PW	:	Purified Water

RCC	:	Reinforced Concrete cement
MGF	:	Multi grade filter
OBR	:	Output between regeneration
FRP	:	Fibre reinforced plastic
EDI	:	Electro deionization
TOC	:	Total organic carbon
VFD	:	Variable Frequency Drive

10 Revision History

Date	Revision	Reason for Revision
	00	New Document