Risk Assessment Document

For

WFI Generation, Storage & Distribution System

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RISK ASSESSMENT FOR WATER FOR INJECTION

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 WFI Generation, Storage & distribution System, which shall consist of the following main components:

- Multi-effect distillation Still
- Condensers
- WFI Storage tank
- Discharge pump
- Distribution loop system
- Control System
- Instrumentation / equipment for process control, monitoring and recording

WFI generation system shall have Purified water as the source water. The system adopts multi-effect still for converting the purified water to WFI. The first column receives black/plant steam as source of external energy to convert the purified water to pure steam in the subsequent columns. The spiral construction provided on the shell gets rid of impurities and endotoxins. The resultant clean steam and distillate are cooled to required temperatures and then led to WFI storage tank.

WFI system is well equipped with high level of automation. The system has control systems on PLC.

Main utilities used for the system operation are Purified Water, Plant steam, Compressed Air, Cooling water and Electrical supply.

Most of the possible risk concerning the handling/ operation of the WFI 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.
- The output/ results of the risk management process should be reviewed to take into account new knowledge and experience.

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  The output/ results of the risk management process should be reviewed to take into account new Knowledge and experience.

  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.

Level	Descriptor	Example detail description
		• 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 WATER FOR INJECTION

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								Mitigation Method (9a)	Residual risk level (9b)	Test Document (9c)	
WFI Generation System											
1.	WFI generation system	High Conductivity of feed water	Yes	Purified water which is a source of WFI, if has high conductivity may challenge the WFI Generation system performance.	No	NA	High	• Conductivity sensor should be installed on the supply line of purified Water. • Provide auto – dumping of feed water in case of high conductivity. • Generation system should stop with Alarm in case of continuous high conductivity.	Acceptable	IQ & OQ	
2.	WFI generation system	Very high flow rate of feed water	Yes	Incomplete evaporation may lead to endotoxin contamination.	No	NA	High	• Flow rate shall be optimized and controlled. PID valve should be installed on the feed water inlet line so as to control the flow of feed water with respect to plant steam pressure. • Automatic draining of extra feed water from distillation column. • Level sensor control on first and last distillation column • Alarm provision in case of high level of water in first or last column.	Acceptable	IQ & OQ	
3.	WFI generation system	Low feed water flow	No	Does not impact the quality of WFI	Operational	WFI generation will be less. Feed pump will run dry.	Medium	• Pressure switch to be installed on feed water inlet line along with alarm provision. • Feed pump should stop in case of low feed water pressure.	Acceptable	IQ & OQ	
4.	WFI generation system	High hardness cooling water is used in condensers for cooling of WFI, leading to formation of scales inside condenser.	Yes	WFI can be contaminated due to damage in cooling water pipes	Operational	Higher hardness of cooling water may lead to lower cooling efficiency.	Medium	Regular preventive maintenance of WFI generation system should be performed as per SOP.	Acceptable	SOP	

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5.	WFI generation system	Lower Heat transfer area	No	No impact on quality	Operational	Lower WFI generation. Feed water loss.	Medium	Provide heat exchangers or other suitable arrangement for preheating of feed water before entering first distillation column.	Acceptable	IQ	
6.	WFI generation system	Higher WFI conductivity	Yes	Performance failure of the system.	No	NA	High	• Test for system performance and all dependent parameters during qualification. • Conductivity sensor shall be provided on WFI outlet. • Provide dumping valve coupled with conductivity meter at WFI outlet so as to dump WFI in case of high conductivity. • Alarm provision.	Acceptable	IQ & OQ	
7.	WFI generation system	WFI Generation Starts After Long Stop In Discharge Line	Yes	Performance failure of the system.	No	NA	High	• Drain valve should be provided to bleed WFI feed point. • Water should drain in case of generation system stoppage time is more. • Hold time study should be performed at the time of qualification activities.	Acceptable	IQ, OQ & PQ	
8.	WFI generation system	Low temperature WFI generated	Yes	For microbiological control a higher temperature of approx. >80°C is required.	No	NA	High	• Flow rate of cooling water shall be optimized and controlled. Pressure Switch or PID Valve should be installed on the cooling water inlet line so as to control the flow of cooling water with respect to WFI outlet temperature. • Temperature sensor cum transmitter shall be installed at the outlet line with auto-dumping of WFI in case of low	Acceptable	IQ & OQ	

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								temperature. • Alarm provision.			
9.	WFI generation system	High temperature WFI generated	No	For microbiological control a temperature of approx. >80°C is required. Hence no impact on quality.	Operational	The WFI generated may start converting into steam at higher temperature leading to loss of water.	Low	• Flow rate of cooling water shall be optimized and controlled. Pressure Switch or PID Valve should be installed on the cooling water inlet line so as to control the flow of cooling water with respect to WFI outlet temperature. • Temperature sensor cum transmitter shall be installed at the outlet line. • Alarm provision.	Acceptable	IQ & OQ	
10.	WFI generation system	Lower WFI tank capacity	Yes	Not sufficient to hold the required volume as per design.	No	NA	High	WFI storage tank should be of appropriate capacity as per design.	Acceptable	IQ	
11.	WFI generation system	Steam leakage on tube side of distillation column	Yes	Product contamination	EHS	Safety Hazards for personnel	High	• Hydrotest must be performed for each column to ensure system integrity. • Vendor to provide report for the same.	Acceptable	IQ	
12.	WFI generation system	No sampling point	Yes	Basic GMP requirement for testing of WFI quality.	No	NA	High	Sampling point to be provided at feed water inlet and final WFI outlet for collection of WFI sample.	Acceptable	IQ	

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13.	WFI Generation system	Water stagnant in the transfer line from WFI generation to WFI storage tank	Yes	Bio film formation may take place, leading to contamination of WFI.	No	NA	High	• Proper slope should be given from the WFI outlet point of generation system to WFI storage tank. • Auto valve should be installed at the tank inlet so that any water remaining in the line after stoppage of generation system should be drained.	Acceptable	IQ	
STORAGE AND DISTRIBUTION OF WFI											
14.	WFI Storage System	No storage of WFI before use.	No	The water quality shall not be affected if not stored.	Operational	• Difficulty in catering to simultaneous demand of multiple user points. Very high capacity of generation system may be needed. • Load on generation system for continuous operation.	Low	• The WFI generated shall be stored in a storage tank of sufficient capacity. • The WFI from the storage tank shall be distributed to the user points through distribution loop and returned back to WFI storage tank	Acceptable	IQ & OQ	
15.	WFI Storage System	Insulation not proper	Yes	Will lead to heat losses to environment. The WFI temp. inside tank would decrease. However for microbial control a temperature of approx.>80°C is required	EHS	The outside surface would be too hot risking operator safety	High	Insulation should be provided with SS 304 cladding.	Acceptable	IQ	
16.	WFI Storage System	No arrangement for controlling of WFI temperature inside tank	Yes	The WFI temp. inside tank would decrease. However for microbial control a temperature of approx.>80°C is required	No	NA	High	• Plant steam supply should be provided to the storage tank jacket. • Temperature sensor should be provided for monitoring and controlling of WFI temperature inside tank.	Acceptable	IQ & OQ	

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								• Alarm provision in case of low plant steam pressure/ temperature and WFI temperature low.			
17.	WFI Storage tank	Leakage in tank	Yes	Contamination of WFI possible	No	NA	High	• Hydrotest shall be conducted for the tank at the vendor's site. Vendor to provide the certificate for the same. • For distribution pipelines, Hydrotest/ Pressure leak test should be conducted by the vendor on site after installation.	Acceptable	IQ	
18.	WFI Generation Storage System	Too much condensate in Plant steam	Yes	Too much condensate will decrease the heating capacity of Plant steam, leading to decrease in WFI temp.	No	NA	High	Proper steam trap assembly is to be provided on the plant steam line with moisture separator.	Acceptable	IQ	
19.	WFI Storage System	Low water level in the storage tank.	No	Low level would lead to unnecessary running of pump and distribution loop running empty.	Operational	No water in the tank, the Pump will run dry. It may damage the pump and affect the process.	High	• The WFI storage tank shall be provided with rope type capacitance level transmitter for monitoring of water level with 4 levels i.e. High-High, High, Low & Low Low. • Discharge pump should turn off in case of low-low level in tank. • Pump should re-start only after tank level has reached low level. • Alarm to be provisioned in case of low & low –low level.	Acceptable	IQ & OQ	

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20.	WFI Storage System	Overflow of WFI from storage tank.	No	Over flow water shall not affect the water quality	Operational	• Overflow of excess WFI requires frequent cleaning of the area. • Loss of resources in form of WFI.	Low	• Rope type capacitance level transmitter shall be provided for monitoring and controlling of water level with 4 levels i.e. High-High, High, Low & Low-Low. • Alarms shall be provided for High & High-High level. • In case level reaches high-high level, the WFI generation system should be stopped and when the water reaches high level than only the WFI generation system should start. The Flow diverter valve at the outlet of WFI generation system shall also stop in case of high-high level.	Acceptable	IQ & OQ	
21.	WFI Storage System	Water stagnant in the WFI Storage tank	Yes	Possibility of Microbial growth.	No	NA	High	• Discharge pump should be provided at WFI storage tank outlet to keep the WFI in continuous circulation mode in the storage and distribution system. • Sanitary spray ball (with 360° spray) is considered at the WFI return line inside the tank for continuous wetting of tank internal surface. • Spray ball functionality to be checked during qualification.	Acceptable	IQ & OQ	

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22.	WFI Storage System	WFI could not be drained from the storage tank.	Yes	During sanitization of WFI 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 (diaphragm type) shall be provided for draining of the water from the tank.	Acceptable	IQ & OQ	
23.	WFI Storage System	Vent filter not provided at the breathing nozzle of storage tank.	Yes	Possibility of environmental contamination of WFI.	Safety	Pressure might be developed inside the storage tank	High	Storage tank should be provided with hydrophobic type of vent filter (pore size 0.2 micron) with SS housing and isolation valve.	Acceptable	IQ	
24.	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 near to WFI temperature. • Temperature sensor should be installed on the vent filter housing so as monitor the temperature of vent filter. • Alarm to be provisioned in case temperature of the vent filter is not within the acceptable range. Heater should switch Off in case temperature exceeds high set temperature	Acceptable	IQ & OQ	
25.	Vent Filter	Malfunctioning of electrical heaters	Yes	The desired temperature of vent filter would not be maintained leading to condensation and then possible contamination of WFI.	No	NA	High	• Alarm is provisioned in case of malfunctioning/ damage of heaters of electrically heated vent filter. • Routine maintenance and checking of heaters as per SOP.	Acceptable	OQ & SOP	

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26.	Vent Filter	• Filter integrity failure • Vent filter choking	Yes	WFI contamination possible.	EHS	Pressure might develop inside tank leading to safety hazards	High	• Filter housing should be equipped with ports for integrity test. • Filter integrity test to be carried out at regular intervals. • Isolation valve should be provided for removal/ replacement of vent filter without affecting storage tank integrity. • Pressure Transmitter should be provided on the storage tank for monitoring tank pressure along with alarm provision. • SOP's: Filter tests; Maintenance	Acceptable	IQ/ OQ/ SOP	
27.	Vent Filter	Affected by the high temperature during the sanitization process	Yes	Filter efficiency will decrease leading to further contamination of the WFI.	No	NA	High	Sterilizable grade vent filters should be used.	Acceptable	IQ	
28.	Sight & Light Glass	Sight & Light Glass not provided	No	No impact on WFI quality	Operational	Monitoring of water level inside tank not possible.	Low	Sight and Light glass should be provided in the tank.	Acceptable	IQ	
29.	Sight & Light Glass	Sight & Light glass connection are not sanitary and not leak proof.	Yes	May contaminate WFI inside tank.	No	NA	High	Sight glass & Light glass are provided with the sanitary design with leak proof design.	Acceptable	IQ	
30.	WFI Distribution	• WFI stagnancy in the distribution line to different user points. • No sampling point	Yes	• WFI 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 WFI distribution shall be in a closed loop system. The water shall be in continuous flow in the loop. • All pipelines shall have drainable slope of > 1:100.	Acceptable	IQ	

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		provided						• 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) • Sampling points shall be provided at all user points in addition to sampling point at storage tank outlet and return line..			
31.	WFI 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 m/s) will be maintained in the loop at return line. • Flow transmitter will be considered on the return line with VFD connection to the discharge pump. • Pressure indicators should be installed at discharge pump outlet and in return loop for monitoring of pressure. • Alarm provision to be provided in case of low flow rate in return loop.	Acceptable	IQ & OQ	
32.	WFI distribution	High WFI conductivity in return line	Yes	Performance failure	No	NA	High	• Conductivity sensor cum meter to be installed on return line to tank. • Provide auto-dumping valve coupled with conductivity meter. • Alarm provision in case of high conductivity. • System should stop in case of continuous high conductivity.	Acceptable	IQ & OQ	

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33.	WFI 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	
34.	WFI distribution	Pipelines are not passivated.	Yes	High temperature water may impact the material and in turn WFI will be contaminated	No	NA	High	Pipeline shall be passivated before being used.	Acceptable	IQ	
35.	WFI Distribution Temperature	Temperature of WFI is too hot for personnel usage.	No	WFI temperature does not have any impact on water quality.	Operational	In processes where manual cleaning is required, personnel may not be able to use hot water for cleaning purpose.	Low	Precaution or instructions should be mentioned in SOPs at the sampling of WFI & usage of WFI in cleaning & other purpose.	Acceptable	SOP	
36.	WFI Storage & Distribution System	Too low or high temperature in return loop	Yes	The WFI temperature inside storage tank may be reduced which may increase bio-load in WFI.	No	NA	High	• Temperature sensor should be installed in the return line which should control the opening and closing of the Steam inlet valve to storage tank for subsequent heating of WFI. • Alarm provision to be provided in case of low WFI temperature.	Acceptable	IQ/ OQ	
37.	WFI Storage & Distribution System	Standby pump is permanently connected to the WFI storage tank outlet	Yes	Stagnant water in pipe connection of standby discharge pump leading to WFI contamination	No	NA	High	Provision should be provided to connect only one discharge pump at one given time to the storage tank.	Acceptable	IQ	

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38.	WFI Storage & Distribution System	Discharge pump selected is of low capacity.	Yes	The minimum required change over (>1) is not achieved. Risk of bio-film formation in the tank due to insufficient water changes.	No	NA	High	Capacity of circulation pump selected should be more than the storage tank volume.	Acceptable	IQ	
Equipment Construction - Internal Surface											
39.	Surface	Internal surface/ contact parts is not compatible with the WFI	Yes	Internal surface may react with WFI and may lead to the WFI contamination	No	NA	High	• Metallic critical contact surfaces (piping, storage tank for WFI) shall be constructed of 316 grade stainless steel or better, electro polished or orbitally welded. • Contact parts of all instruments, level sensors, valves etc, shall be of SS 316 or better. • Supporting structure and non contact parts inside clean room shall be of SS 304 or better. • Diaphragm Valves: SS 316 or better, electro polished. • WFI distribution pipeline shall be of SS 316 or better.	Acceptable	IQ	
40.	Polymeric materials	Polymeric materials are not compatible and are not replaceable	Yes	Polymeric ,material may react with WFI and lead to contamination	No	NA	High	• Gaskets and O-rings coming in direct / indirect contact surfaces shall be made up of food grade polymeric materials only and shall be high temperature & pressure resistant. • The easy change of gaskets must be possible. • Vendor shall provide the certificate for food grade polymeric material.	Acceptable	IQ	

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								Mitigation Method (9a)	Residual risk level (9b)	Test Document (9c)	
41.	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 and thereby leading to WFI contamination	No	NA	High	• All welds shall be ground finished and properly passivated and orbital welding should be done. • Welding to be done using high purity argon gas. • Vendor to provide certificate for the same. • 100% Boroscopy test shall be performed for confirmation of the same.	Acceptable	IQ	
42.	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 ≤ 0.8 µm Ra. • The surfaces should be grounded to a smooth finish without any sharp corners and crevices.	Acceptable	IQ	
43.	Joints	Joints are leaking	Yes	May lead to WFI contamination.	No	NA	High	• Suitable gaskets shall be provided for air tight connection which shall be replaceable. • Quick release Triclover joints are recommended.	Acceptable	IQ	
44.	Valves for clean media	Not of hygienic (sanitary) design	Yes	Contamination of WFI possible	No	NA	High	All valves coming in contact with feed water and WFI shall be of hygienic design. They should be installed at drainable angle and shall have weep hole.	Acceptable	IQ	

Equipment Construction - External Surface

RISK ASSESSMENT FOR WATER FOR INJECTION

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)	
45.	Surface	External surface of parts installed inside clean room is not suitable	Yes	May lead to the clean room contamination	No	NA	Medium	Supporting structures and frames shall be SS 304.	Acceptable	IQ	
46.	Finishing	External finish of parts installed inside clean room 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 or mirror finished	Acceptable	IQ	
PLC/Control System											
47.	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	
48.	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	
49.	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	
50.	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	
51.	Man-machine Interface	Monitoring/recording and documentation of GMP relevant	Yes	Basic GMP requirement	No	NA	High	• It should be possible to monitor/record GMP relevant	Acceptable	OQ	

RISK ASSESSMENT FOR WATER FOR INJECTION

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								Mitigation Method (9a)	Residual risk level (9b)	Test Document (9c)	
		data not possible						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.			
52.	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	
53.	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 WFI Generation, Storage & Distribution System'.	Acceptable	OQ	
54.	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	

RISK ASSESSMENT FOR WATER FOR INJECTION

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								Mitigation Method (9a)	Residual risk level (9b)	Test Document (9c)	
55.	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	
56.	Accessibility to PLC	Parameter settings not identified universally	Yes	Basic GMP requirement	No	NA	High	Parameters settings should be in numeric only.	Acceptable	OQ	
57.	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	
58.	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 WATER FOR INJECTION

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)	
59.	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	
60.	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	
61.	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	
Utilities											
62.	Compressed air	Insufficient pressure	Yes	Improper functioning of pneumatic instruments/ components may lead to improper functioning of the system.	No	NA	High	• Pressure gauge/ Pressure switch should be provisioned at compressed air inlet to monitor & control compressed air pressure along with alarm provision. • System should stop in case of low compressed air pressure.	Acceptable	IQ & OQ	

RISK ASSESSMENT FOR WATER FOR INJECTION

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								Mitigation Method (9a)	Residual risk level (9b)	Test Document (9c)	
63.	Plant Steam	Low plant steam pressure and temperature	Yes	Incomplete evaporation.	Operational	Loss of excess feed water	High	• Pressure gauge/ Pressure switch should be provisioned at plant steam inlet line. • Alarm provision in case of low pressure or low temperature.	Acceptable	IQ & OQ	
64.	Plant Steam	Too much condensate in Plant steam	Yes	Too much condensate will decrease the heating capacity of Plant steam, leading to decrease in WFI output.	No	NA	High	Proper steam trap assembly is to be provided on the plant steam line with moisture separator.	Acceptable	IQ	
65.	Cooling Water	Cooling water supply low	Yes	High temperature WFI shall be generated.	Operational	WFI temperature will increase.	Medium	• Pressure switch to be provided on cooling water inlet line. • Alarm provision to be provided in case of low pressure. • Alarm provision in case of high temperature cooling water at the return line.	Acceptable	IQ & OQ	
66.	Cooling Water	Cooling water flow rate high	Yes	Low temperature WFI is generated	No	NA	High	• Flow meter shall be installed on the cooling water inlet line to regulate the cooling water flow OR Proportionate control valves shall be installed for controlling the flow of cooling water based on WFI temperature. • Low temperature WFI shall be drained before going to the WFI storage tank.	Acceptable	IQ & OQ	

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								Mitigation Method (9a)	Residual risk level (9b)	Test Document (9c)	
System Cleaning and sanitization											
67.	Cleaning	Difficult cleaning	Yes	Accumulation of particles, contamination of clean room possible	No	NA	High	• The design of the complete shall ensure adequate clean ability (smooth, SS316 or better surface). • Parts which are required for cleaning should be provided with quick fixing arrangement. • All bolts, nuts on the exterior part of equipment will be with dome nut.	Acceptable	IQ	
68.	WFI Storage tank & Distribution System	Sanitization/ Sterilization not possible	Yes	In case of biofilms formation in the WFI storage & distribution system, it cannot be removed.	No	NA	High	• A suitable SIP process shall be provided in the PLC for effective sanitization of the storage tank and distribution system. • Pure steam supply should be provisioned to the storage tank for Sanitization. • Tank and distribution lines shall be insulated to prevent loss of heat during sanitization. • Alarm to be provisioned in case of High/ low temp. during sanitization. • Air Line should be provided in jacket to empty out the jacket after sanitzation.	Acceptable	IQ & OQ	
69.	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	

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70.	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											
71.	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	
72.	WFI 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	

RISK ASSESSMENT FOR WATER FOR INJECTION

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								Mitigation Method (9a)	Residual risk level (9b)	Test Document (9c)	
System Safety											
73.	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	
74.	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 75 db from 1m from the system.	Acceptable	OQ	
75.	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 WFI generation as well as distribution system.	Acceptable	IQ & OQ	
76.	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 (generation as well as storage) should be defined. • Warning stickers on all hot surfaces must be provided to protect personnel, product and equipment. • Elevated temp. & pressure should be alarmed leading to the opening of the safety valve at both generation and storage system.	Acceptable	IQ & OQ	

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77.	WFI Generation and Distribution System	High emission of heat	Yes	Disturb room temperature and relative humidity.	EHS	Environment & Personnel safety hazards	High	• Proper insulation should be provided around tank & on distribution lines. • SS 304 cladding should be provisioned for insulation. • Insulation material should be resin bounded Glass wool/ Rock wool.	Acceptable	IQ	
Documentation											
78.	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	
79.	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	
80.	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	

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81.	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. WFI 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
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
WFI	:	Water For Injection
TOC	:	Total organic carbon
VFD	:	Variable Frequency Drive

10 Revision History

Date	Revision	Reason for Revision
	00	New Document