Clean Media System

Water – where does it come from

- Portable water is the prescribed initial source for the production water.
- The use of other water systems must include a documented rationale based on site specific validation, monitoring, and/ or testing programs
- Up to date water systems must be installed in all new Pharma manufacturing facilities

General System Design Criteria

- Aspects to ensure proper operation of the water systems:
    - Dead legs must be minimized
    - Turbulent flow must be established in all parts of the system, specifically, return flows of loop systems
    - Positive pressure differential must be maintained from the loop system to the point of use
    - Adequate slope of piping towards drains must be established
    - Air breaks to the waste water system and, where applicable, the condensate system, are required

Production Methods – Overview

- Ion Exchange
- Reverse Osmosis (RO)
- Electrodeionization (EDI) or continuous electrodeionization (CEDI)
- Ultrafiltration
- Distillation

1. *Ion Exchange*

- Ion exchange is suitable to produce Purified Water (PW) out of potable water.
- It normally consists of four main steps.
    - The first step is a cation exchanger that removes cations like Ca2+, Mg2+ and Na+.
    - Downstream of the cation exchanger, a degasifier removes CO2.
    - In the third step, anions like CO3 2-, SO4 2- and Cl- are removed.
    - The final purification step is a polishing step and is either a multistep- or mixed bed ion exchanger.
- Final filtration must be performed to prevent particles from getting into the distribution system.

2. *Reverse Osmosis (RO)*

- Reverse osmosis may be used to produce PW out of potable water.
- Pre-treatment of the potable water upstream of the RO is recommended to prevent scaling on the RO membranes.
- To meet the conductivity requirements it is necessary to either combine two RO stages on the permeate side (two pass RO) or use a combination of RO and electro- deionization (EDI).
- Depending on the potable water quality, a two pass RO may not be sufficient to meet the PW quality requirements for conductivity.

3. *Electrodeionization (EDI) or continuous electrodeionization (CEDI)*

- Electrodeionization or continuous electrodeionization is used in combination with RO or ion exchange either to produce PW or Highly Purified Water (HPW) / WFI.
- The EDI / CEDI is a polishing step and removes the remaining ions passing the RO / ion exchange

4. *Ultrafiltration*

- Ultrafiltration is used to reduce the microbiological load and remove endotoxin.
- The cut off of UF modules must be <20kDa.
- Ultrafiltration is the preferred method of HPW production.
- Water for Injection may be produced using ultrafiltration per the USP and JP; however, it WAS not an acceptable method for WFI production according to the EP until April 2017. Since April 2017 it is a acceptable method.

5. *Distillation*

- An appropriate method should be used to produce WFI. The preferred method is distillation. Alternative methods, such as RO, may be considered.
- Either vapor compression or multi-effect may be utilized.
- A degasification step may be part of the distillation process to increase product safety and quality of WFI dependent on the feed water.

Water-specification

Quality requirement

- Specifications
  - Requirements are clearly specified in pharmacopeias
  - Where specific commitments have been made between company, regulatory authorities, and/or business partners, these requirements must be adhered to
- Testing Requirements
  - water systems must be qualified to meet the pharmacopeial requirements
  - All water systems must meet applicable pharmacopoeia standards for chemical and microbial purity
  - The testing requirements common to all pharmacopeia are defined in the tables below.

HPW = Highly Purified Water

- HPW was introduced January 2002, to offer alternative methods to destillation for example for production of high amounts of cleaning water in «WFI-quality».
- Reverse Osmosis or UltraFiltration are the two accepted methodes.
- The use of different qualities of water is clearly defined
- The monographia for higly purified water (HPW) was withdrawn in April 2019 from European Pharmacopeia. The advantages and the risks of a cold WFI production by membrane techniques are beeing discussed extensively. Systems are still in use in industry!

Final Purification Step for Water Production

Final Purification Step	USP		EP			JP	
	PW	WFI	PW	HPW	WFI	PW	WFI
Ion Exchange	✓	–	✓	–	–	✓	–
Reverse Osmosis	✓	✓	✓	–	–	✓	–
EDI	✓	–	✓	✓	–	✓	–
Ultrafiltration	✓	✓	✓	✓	–	✓	✓
Distillation	✓	✓	✓	✓	✓	✓	✓

Final Purification Step	USP		EP		JP	
	PW	WFI	PW	WFI	PW	WFI
Ion Exchange	✓	–	✓	–	✓	–
Reverse Osmosis	✓	✓	✓	✓	✓	✓
EDI	✓	–	✓	–	✓	–
Ultrafiltration	✓	✓	✓	✓	✓	✓
Distillation	✓	✓	✓	✓	✓	✓

Final Purification Step	USP		EP		JP	
	PW	WFI	PW	WFI	PW	WFI
Ion Exchange	✓	–	✓	–	✓	–
Reverse Osmosis	✓	✓	✓	✓	✓	✓
EDI	✓	–	✓	–	✓	–
Ultrafiltration	✓	✓	✓	✓	✓	✓
Distillation	✓	✓	✓	✓	✓	✓

Generation of WIFI (Destillation)

Design Criteria

- The design criteria for WFI Systems are typically described in detail in the system's User Requirements Specification (URS) document
    - Primary focus:
        - system performance requirements
        - particular attention to the water quality monitoring
        - control during WFI generation, storage and distribution
    - producing water for pharmaceutical use is to ensure
        - constant, reliable and suitable water quality
- the method chosen shall guarantee a constant quality of water even when boundary conditions change

System Architecture

- WFI Systems consist of three main parts
    - Generation
    - Storage
    - Distribution
- Generally a water system has several pretreatment steps and one final step
- Pretreatment includes process steps or unit operations occurring prior to the final water treatment step.
- It is a series of unit operations to modify the feed water quality so that it will be of adequate quality to be fed to a final treatment step
- Pharmaceutical water systems are required to use feed water that complies with drinking water standards

Contamination prevention and safeguard water quality

- To prevent potential WFI contamination and to safeguard water quality the following system design aspects must be taken into account
    - Dead legs must be minimized to avoid stagnant water and lack of thermal and chemical penetration
    - Turbulent flow must be established in all parts of the system, including return flows of loop systems. Turbulent return loop flow may not be required during periods of high use, depending on the system design requirements
    - Positive pressure differential must be maintained in the distribution loop from the loop system to the points of use and sample valves
    - Adequate slope of piping towards drains (point-of-use valves, sample valves, low point drains) must be established
    - Air breaks to the waste water system and, where applicable, the condensate system are required
    - Materials of construction must not leach extractables or shed particles under the intended operating conditions

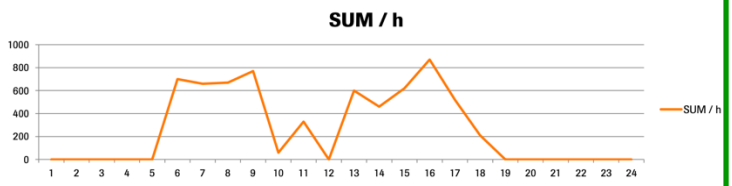
Performance Requirements System Capacity

- Design based on the User Requirements (or similar doc) to ensure non- interrupted operations
- At minimum, requirement should take in consideration following factors:
    - Minimum and maximum required WFI demand in the system based on the facility production schedule
    - Required system / components redundancy
    - Number of point-of-use valves and their location throughout the facility
    - Number of point-of-use valves that require hot and (or) cold / ambient WFI
    - Minimum and maximum allowed pressure and/or flow at each point-of-use
    - Maximum allowable downtime for routine maintenance
- These and other factors should be used to determine the generation system, storage tank capacity, type and number of distribution loops and point-of-use valves in each loop

- Production starts at 6:00h with a filled 5m3 tank. WFI destill produces 0.5m3/h. Production starts with a 30 min cleaning step at 6.30h, equipment washer starts 1h later, vial washing process starts parallel. Filling of vials starts at 7:30h for 6 hours. After filling another cleaning step takes place for 30 minutes. The day ends with a equipment washing process at 15:00h for 1h.
- Fill the table, calculate sum of WFI needed per hour
- When is tank level minimum?
- When ist tank full?
- Draw a graph of the sum WFI

Water needed – production schedule

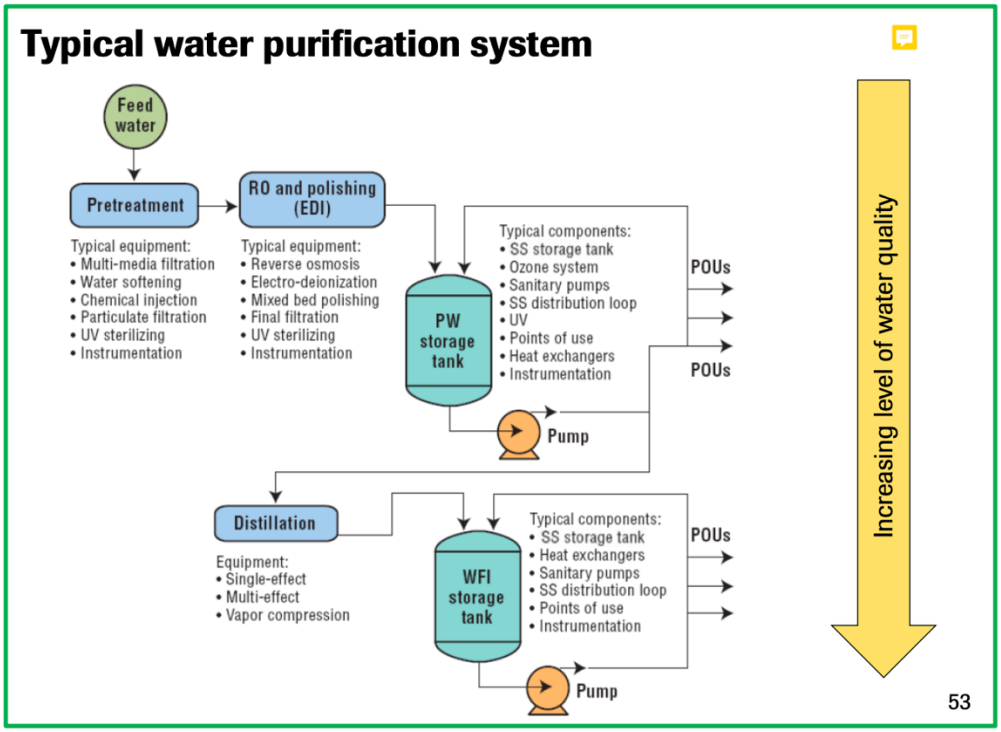
Equipment / hour	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
Washing Machine						100	200		200		200				200	200	200	200						
Manual Cleaning						100	100	100	50	50	50		100	100	100	100								
Vial Washer						300	300	300						300	300	300								
Ultrasonic Bath						200			200				200			200								
Autoclave									300				300				300							
Equipment x								200																
Equipment y								10	20	10	20				20	10	20	10						
Equipment z							60	60			60			60		60								
SUM / h	0	0	0	0	0	700	660	670	770	60	330	0	600	460	620	870	520	210	0	0	0	0	0	0



Same for: hot use / cold use

WFI (Water for Injection) Quality Attributes

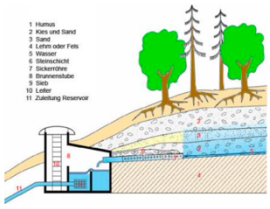
- Water for injection (WFI) is used in parenteral formulations
  - as a constituent of the final pharmaceutical product
  - as a component
  - As a cleaning agent in the production stages
  - in the production of active ingredients where there is a risk of endotoxin contamination
- The limits regarding conductivity and the number of organisms allowed in WFI are lower than those for Purified Water (PW). In addition, there is an endotoxin limit.
- The European Pharmacopoeia stipulates that the last step in WFI production must always be a distillation or reverse osmosis
- Every pharmacopoeia (EP, USP and JP) stipulate that input feed water for the production of WFI quality water must comply with the national regulations regarding drinking water
- Quality requirements for drinking water are defined in national or regional ordinances
- Compliance with these requirements can be demonstrated either by certificates of analyses issued by the water provider or by suitable monitoring of the pharmaceutical manufacturer

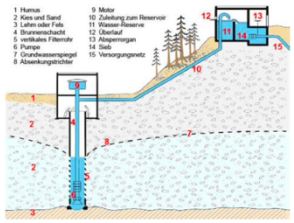


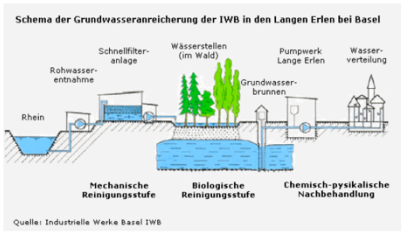
Feed Water Quality

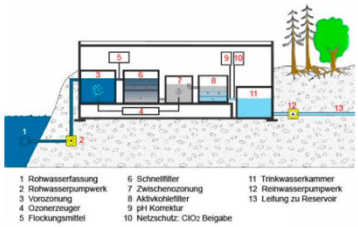
- Identification of the required pretreatment and subsequent process steps should be based on information about the feed water quality.
- Complete analyses are often available from the local water provider.
- These analyses are averages and will not always provide information on seasonal variations or changes in quality owing to transport through the suppliers distribution system.
- Consequently, the designers should use water analyses from samples drawn over the year at the location where the WFI system is to be built.
- For planning purposes, the following parameters should be recorded and analyzed on a monthly basis.

Feed water, different sourcing ground, source, river, sea

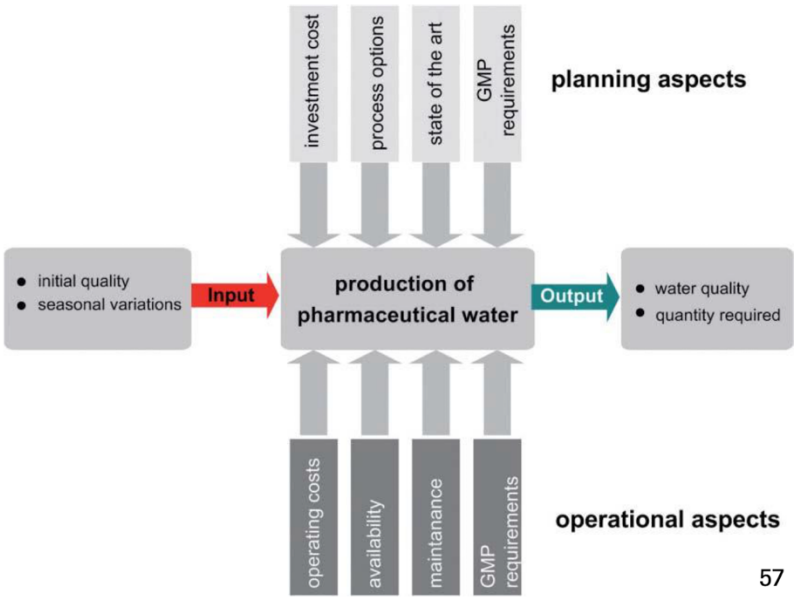








Parameters influencing system planing



WFI Generation – summary !!!

- WFI is the purest grade of bulk water and must be used for the manufacture of parenterals, some ophthalmic and inhalation products, and for finishing steps of parenteral grade active pharmaceutical ingredients (API's).
- As a matter of principle, three different final purification steps are allowed according to USP, Japanese Pharmacopoeia JP and the European Pharmacopoeia EP.
- Distillation systems are recommended for the final WFI purification step within manufacturing but other methods are allowed.
- The pharmaceutical distillation chemically and microbiologically purifies water by phase changes and entrainment separation. In this process water is evaporated, producing steam. The steam disengages from the water leaving behind dissolved solids, non-volatiles, and high molecular weight impurities. Low molecular weight impurities are carried with the water as mist and/or droplets, which are entrained in the steam. A separator removes fine mist and entrained impurities, including endotoxins. The purified steam is then condensed to product WFI.
- A degasification step may be part of the distillation process to increase product safety and quality with respect to volatile organic compounds, or gases like carbon dioxide.

Final Purification Step	USP		EP		JP	
	PW	WFI	PW	WFI	PW	WFI
Ion Exchange	✓	–	✓	–	✓	–
Reverse Osmosis	✓	✓	✓	✓	✓	✓
EDI	✓	–	✓	–	✓	–
Ultrafiltration	✓	✓	✓	✓	✓	✓
Distillation	✓	✓	✓	✓	✓	✓

Use of different water qualities – A cost comparison

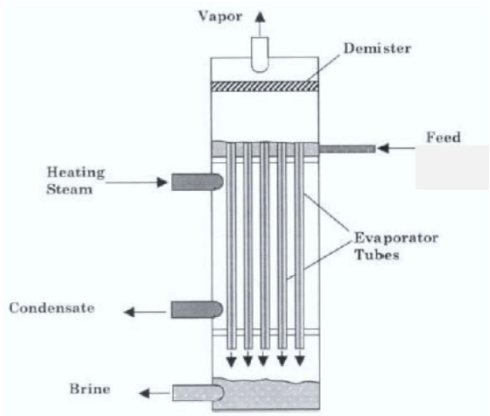
Potable water (cost factor 1x)	Purified water (cost factor 5x)	WFI (cost factor >10x)
- technical use - feed water - manufacturing of substances (chem.) - cleaning rooms - primary cleaning equpments	- pharmaceutical use - cleaning of equipment	- pharmaceutical use - cleaning of equipment (final rinse)

Cos comparison – production of water

Membrane Systems	Destillation Systems
• Low cos • Good purge of endotoxin • Low energy consumption • 25% purge • Low amount of cooling water • No clean steam production possible • Water is immediately available • Nor corrosion • No pressurized tank • Membrane are difficult in use •	• High cost • Good purge of endotoxin • High energy consumption • 10% purge • Cooling water needed at point of use • Production of clean steam is possible • Time needed for production • Corrosion can be problematic

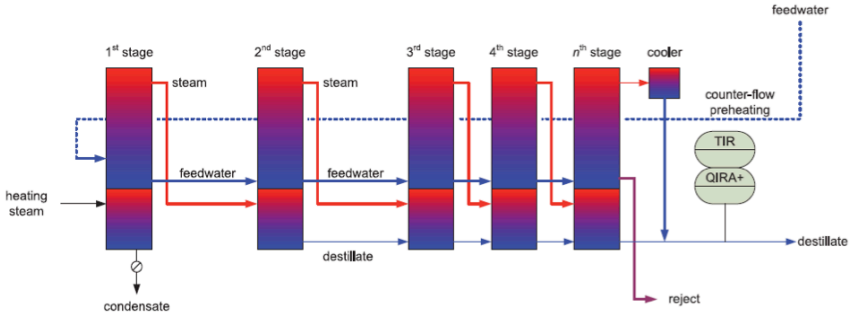
Destillation Medthods

1. ***Single – Effect Distillation***



- Single-Effect Distillation incorporates a single evaporator heat exchanger, a separator mechanism, and a condenser. Systems are available in electrically or steam powered versions, although electrical units are limited to very small production rates (~250 liter per hour).
- There are different types of evaporation systems for stills. A common type is a tubular falling film evaporator.
- The inlet for feed water is on top of the column. Inlet water is distributed inside the evaporation tubes.
- A fine water film on the surface of the evaporation tubes is necessary.
- Evaporation progressively takes place from top to bottom.

2. ***Multi – Effect Distillation***



- Multi-Effect Distillation systems incorporate two or more evaporator heat exchangers, separator mechanisms, and a condenser into a staged evaporation and condensation process.
- Current distillation systems usually rely on pressure stages to allow high energy efficiency.
- The steam generated from feedwater in the first column is used to heat the second column. The condensate is the heating steam condensate. The steam generated in the second stage is used to heat the third, and so forth.
- The condensate produced from generated steam in the cooler is the distillate (WFI).
- Due to the cascading flow, the pressures in the columns differ. The number of stages is optimized with regard to investment and operating costs. The greater the number of columns producing greater thermal efficiency and savings from plant steam consumption, but resulting in greater initial capital investment.
- A common misconception about multi-effect distillation is that each column further purifies the WFI. In reality, the WFI generated as distillate from the first column is the same purity as that from the last column.
- Systems having four to seven stages are typical.

3. ***Vapor Compression Distillation***

- Vapor Compression is a distillation method where water is evaporated inside, or outside, a bank of tubes arranged in a horizontal or vertical configuration. The horizontal design is normally of the forced circulation type with a recirculation pump and spray nozzles creating a falling film over the tubes. The vertical design is of the natural circulation type with the bottom portion of the tubes submerged. Major system components include the evaporator, compressor, heat exchangers, de-aerator, pumps, motors, valves, instruments and controls.
- Vapor Compression operates on the same principle as the mechanical refrigeration cycle. In a Vapor Compression still, feed water is evaporated on one side of the tubes. The generated steam passes through the disengagement space, through the separator, and into the compressor.
- The energy imparted by the compressor results in compressed steam with increased pressure and temperature. The higher energy steam is then discharged back into the evaporator / condenser vessel. The steam condenses and gives up its latent heat, which is transferred through the tube wall to the water. More water is boiled off, generating more vapor, and the process is repeated. The outgoing distillate and blow down streams preheat the incoming feed water, thus saving energy. Because the latent heat is recycled, there is no need for a stand-alone condenser as in the Single-Effect or Multi-Effect systems.

Influencing Parameters to be considered

I. WFI vs. PW System
   i. The system designer should consider the required volumes of clean utilities needed in the facility. Determine if the system will be primarily WFI or PW based. If there is only a small need for PW, it may be more effective to couple a vapor compression unit with minimal pretreatment and use the WFI for both applications. If only a small consumption of pure steam is needed it could be more advantageous to tap pure steam from a Multi-Effect still than the additional investment of a dedicated pure steam generator. If non- condensables are an issue, either distillation method can be provided with a de-aeration process.

II. Maintenance
   i. Multi-Effect still maintenance is comparatively low due to the minimal moving parts; but as part of a good preventive maintenance schedule, it may require descaling on a yearly basis. A vapor compression still will possibly require a more frequent preventive maintenance schedule due to the moving parts, but the advances in newer compressors may help minimize the time required. Vapor compression WFI generators tend to have a higher risk for particulate concerns and leakage due to moving parts in the clean media path.

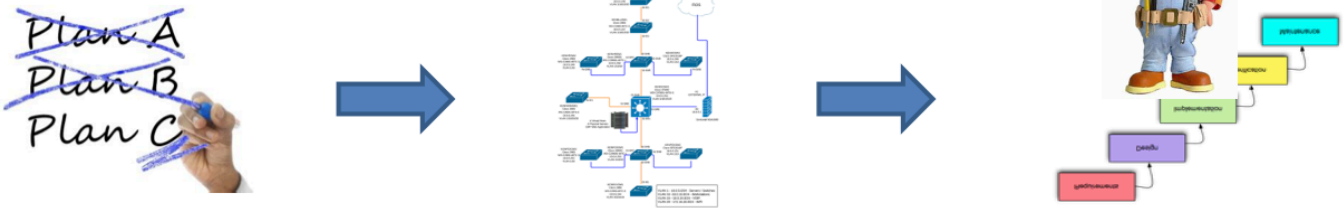
III. Supporting Utilities
   i. The available supporting utilities need to be considered. If steam is not readily available, electric driven models exist with both technologies, but only smaller volumes ≈ 280 l / h are typically appropriate for Multi-Effect design. The need to minimize use of cooling water could also favors the selection of a vapor compression still. However, the consumption of cooling water minimizes with increasing number of columns, too. A PW system already on site could feed a Multi-Effect still, thus taking advantage of the lower acquisition cost as compared to vapor compression.

IV. Space Constraints
   i. Multi-Effect stills generally take up less floor space than a vapor compression still. However, gravity feed to a WFI holding tank may require more additional headroom than is available. If gravity feed of the distillate is not feasible, an additional distillate receiver and pump may be needed to deliver the WFI to the storage tank, which also introduces moving parts, dynamic seals, etc. into the distillate path. Of the two Multi-Effect technologies, falling film type systems tend to be more compact, but taller; whereas the natural circulation method requires more floor space if the external evaporators are installed. In some models, a raised condenser may alleviate full height demands.

Clean Media Planning/ Design Phase

Planning & Realization

How much?, What ? , Where? … Questions should be answered.



Storage and Distribution

- Storage and distribution systems must be designed to adequately distribute and maintain water quality
- New and refurbished water systems must be supplied via a loop system to the points of use
- Three types of storage and distribution systems are common:
    - Cold systems with temperatures < 10 °C
    - Systems with temperatures at ambient conditions
    - Hot systems with temperatures > 70 °C

Storage

- The purpose of a storage system is to buffer peak flow requirements, and consequently, reduce the size of the WFI still
- In systems serving different production units, dedicated storage tanks may be used to separate the various production units, either to avoid cross-contamination or to deliver WFI with different temperatures
- Proper selection of the WFI tank will take into account many factors, including:
    - size
    - pressure rating
    - material of construction
    - storage temperature
    - number and type of connections
    - sprayball requirements
    - sanitization philosophy

Table WFI Generation and Storage Sizing Factors

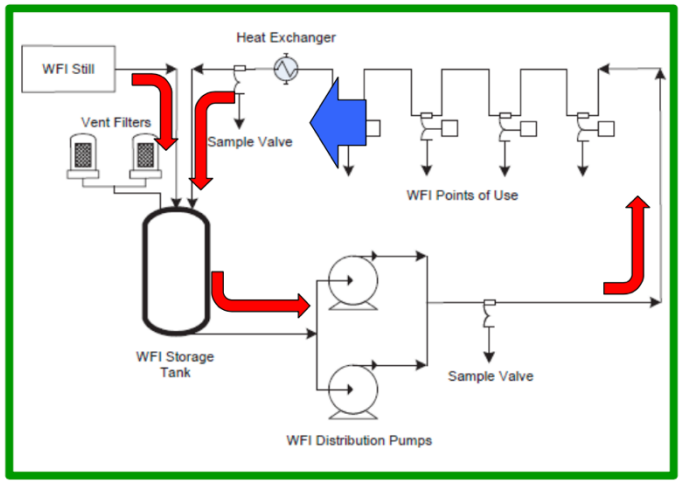
TANK → / GENERATION ↓	TOO SMALL	TOO LARGE
Too Small	• Generation system running continuously • No safety factor in sizing of tank or generation system • High impact to the production schedule	• No safety factor in generation system sizing • Large tank may require more utilities (steam jacket, nitrogen blanket) • Large tank may occupy valuable space • Capital cost for large tank
Too Large	• Capital cost for generation system • Small tank will result in excessive cycling of WFI generation system	• Generation system will often be idle • Capital cost for tank and generation system • Large equipment will occupy more space than necessary • High operating cost (utilities) • Higher cost of replacement parts

Distribution

- WFI is stored in a storage tank and supplied to the point-of-use through a loop which circulates back to the tank. A distribution system typically consists of one or more pumps that convey the water to the consumers via the supply line, and back to the storage tank via the return line.
- A loop system allows sanitizing the system by WFI recirculation through the loop piping and flushing small amount of water through point-of-use valves or sample valves.
- Temperature and flow velocity requirements can be easily met during operating times with little or no withdrawal.
- The storage tank must be operated in a manner that minimizes microbial growth. Conditions where no microbial growth occurs are termed “self-sanitizing”.
- The water system must be designed to allow sanitization.
- System selection is determined by the number of the points of use and their locations in the building
- and by the number of stories and the quantity withdrawn.
- Sizing is primarily determined by consumer requirements in terms of volumetric flow and pressure. Where a consumer requires a temperature differing from that prevailing in the loop, part of the water withdrawn from the loop is cooled or heated using a heat exchanger.
- The consumer can be connected to a sub-loop (secondary distribution), in which water is kept in permanent circulation.

Loop – Serial System

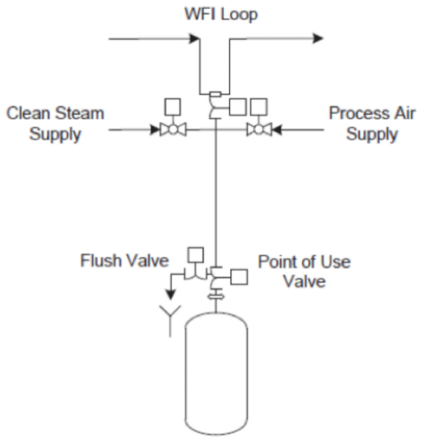
- In a serial system the loop is directly routed to the consumers, with the points of use being connected serially to the loop in compliance with hygienic piping design
- If technically feasible, a series design is generally preferred over parallel design (regarding the number of heat exchangers and number of points of use).
- In series design, the number of subloops (hot/cold points of use) should be limited because of the pressure drop at each sub-loop.



Points of use design

- The consumer must not be able to affect to overall water system quality
- Any backflow and any contamination of the water system, and thus of all other consumers, must be safely excluded by a positive pressure gradient towards the Points of Use and air breaks between point-of-use or sample valves and drain piping
- Four basic phases (or modes of operation):
    - Non-use
    - Preparation for use
    - Use
    - Post-treatment of point-of-use
- It must be ensured that no contamination is bought to the point-of-use from the connecting piping section
    - Possible measures include
        - Connection pipe designed to allow draining of the respective loop section via this point-of-use
        - Connection pipe to be blow dry using a suitable flushing gas
        - Connection pipe to be sanitized with pure stream
        - Connection pipe to be pre-rinsed with water having the required quality
        - In case of need, removable aseptic connections should be provided for separate cleaning procedures

→ The first three measures are illustrated in the example:



WFI Distribution – Point of use management system
Automation and instrumentation

- Fully integrated system (automated control)
- Connected to other plants and their control system electronic data collection, centralized alarm monitoring with recording
- If the WFI quality is not withing specification and / or the pressure/flow in the loops are too low, the management system interlocks the point of use valves automatically

System Capacity/Dimensioning

- Sizing a WFI generation, storage and distribution system must take into account a number of factor, including, but not limited to the following:
    - Space constrains
    - Available utilities

    - Downtime for sanitization/sterilization
    - Downtime for scheduled (or unscheduled) maintenance
    - Energy efficiency/conservation
- A number of tools exist to assist in sizing a WFI system
- Although different approaches will ultimately yield the necessary results, the basic elements of WFI system sizing are always the same

Tank and Tank Design

Tanks

- Many factors determine the design of the WFI storage tank
    - Size
    - Shape
    - Amount of nozzles
    - Configuration
- Vertical storage tanks are most common, but horizontal tanks may be necessary if overhead space is limited
- Tank design details should be discussed with qualified tank manufacturer to meet all requirements, minimum required volume and shape and assure that the vessel can be fabricated in cost efficient way

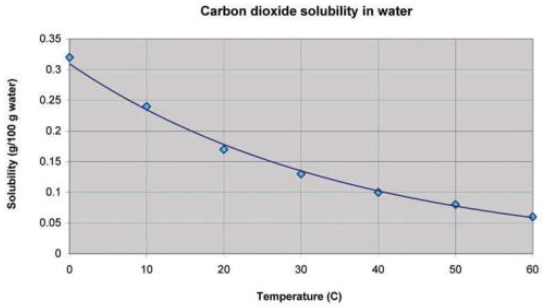
Tank Spraying Device

- It is important to maintain the WFI storage tank interior through continuous spraying. This discourages microbial growth by preventing drops from forming on internal surfaces of the tank headspace.
- Spray balls or other spraying devices should be used for this purpose. Spray device design is based on the required coverage, which is directly related to tank internal diameter, head radius and top nozzles configuration. Tanks with large diameters may require more than one spray ball to ensure complete coverage. Total minimum flow and pressure required for proper operation of the spray balls should be included in the WFI distribution pumps sizing calculation to assure minimum required flow and pressure in the return loop.
- Spray devices should be designed with removable sections to allow their periodic visual inspection. Rotating spray devices are not recommended, due to the continuous service required and the risk of generation of particles.

Tank Headspace Blanking with Nitrogen

To avoid the absorption of carbon dioxide and its effect on conductivity, inert blanketing of the tank headspace may be considered. Storage tanks must be fitted with a sub-micron hydrophobic vent filter to prevent contamination with viable and non viable particles from the surrounding air.

Nitrogen blanketing of storage tanks removes the presence of oxygen in the tank atmosphere. This leads to a drop in the oxygen concentration of the water, reducing the redox potential, which may result in a change in the passive layer.



Insulation

- Whether the WFI storage tank is used for hot or ambient WFI, it will need to be insulated.
    - An ambient WFI tank will likely need to be hot water sanitizable.
    - Both hot and ambient WFI tanks require clean steam sanitization after major maintenance work.
    - The WFI tank should be insulated for heat conservation to minimize utility consumption, as well as for personnel protection.
- The decision to insulate the top head of the WFI storage tank should be considered for multiple reasons, including higher cost.
- The preferred alternative to sheathing (mantle) and insulation on the top head is a removable insulation blanket, which can be installed to provide safe access to nozzles and clamps, as required.

Internal Finish

- internal surface finish should match the internal surface finish of the sanitary piping and fittings used in the distribution loop.
- material 316L Stainless Steel
- mechanically polished to Ra <0.8 µm
- Electropolishing is recommended instead of passivation after mechanical polishing, especially for hot WFI Systems
- Electropolishing is proven to significantly reduce rouging effect and decreases frequency of the tank periodic de-rouging

Exterior Finish

Some common options, in order of increasing cost, are:

- No surface finish – welds are simply “Scotch-Brite” treated quickly to remove surface discoloration.
- Bead blast exterior – entire exterior of vessel is glass bead blasted to give the entire vessel a uniform finish, but welds are still visible.
- Bead-blast welds only – area around weld seams on tank sheathing is masked, and only the unmasked area is bead blasted.
- Mechanical polish of weld seams – usually followed by bead blasting

Filters

- Filters only to be used as vent filters on the WFI storage tanks.
- No inline filters on WFI systems. Risk: breeding ground for microbial growth
- Vent filters on WFI storage tanks
  - 0.2 µm hydrophobic elements
- Sizing criteria for filters relates to Steam-in-Place (SIP) process when air flows into the storage tank to compensate for the volume change associated with steam condensation
  - At the end of SIP procedure, steam in the tank will cool and undergo a phase change to liquid water. The volume difference between the water amounts in gas phase vs. liquid phase is greater than 1000x.

Materials

- WFI storage and distribution systems, which are used in large scale commercial and clinical production facilities, are commonly constructed of 316L or equivalent austenitic stainless steel (UNS S31603, DIN 1.4404 or 1.4435).
- Relatively small size ambient WFI systems, typically used for QC or Research and Development laboratories, may be constructed from PVDF plastic
- The 316L (stainless steel , low-carbon version)
  - commonly available
  - has demonstrated adequate corrosion resistance
  - reasonable fabrication and installation cost
  - when properly cleaned and passivated, stainless steel will develop a protective oxide layer or passive layer which is the primary defense against aggressive ion-hungry PW

Piping

- The WFI piping system should use 316L sanitary tubing for its material of construction.
- Piping system fabrication and installation should follow current ASME / ISO / EN / DIN standards to ensure proper welding procedures are used and adequate slope is achieved for complete system drainability.

Welding of Stainless Steel

Welding should be performed by an autogenous orbital welding process, which fuses the base material without the use of a filler metal.

Basic elements of WFI system sizing – summary

- Determine the usage profile:
  - Interview users to learn minimum and maximum required pressure, flow rates, quantities and times for all WFI usage (this includes periodic sampling, cleaning and “passive” demands such as pump seal flushes, instrumentation slip streams, sanitization flushing, etc.).
  - Use the data to develop a timeline graph of WFI demand. The graph should encompass at least one full “cycle” of demand, or one full interval (such as a production run) that will reflect the peak and minimum demand periods.
- Determine the total amount of WFI required per shift (per day, per week, per run).
- Select a WFI generation system and storage tank that will provide optimal balance between adequate and excess capacity. Some factors that will affect this are:
  - WFI generation systems tend to perform better over time when they are sized to run for longer durations, as opposed to frequent starting and stopping.
  - WFI storage tanks should be sized to maintain a volume of 50-80% during all but the most excessive usage scenarios.
  - WFI storage tanks and generation systems should be sized to achieve as close to a “steady state” operation of the WFI generation system as possible.

Isometric drawings / Isometric projection

Isometric projection is a method for visually representing three-dimensional objects in two dimensions

Clean Steam

Clean Steam use

- for various sterilization processes
  - – primarypackagingmaterial
  - Instruments
  - vessels(SIP)
- for sterilization of the WFI system after maintenance
- for air-humidifying (HVAC) in “critical rooms”

Clean Steam generation

- Use of purified water (WBI) as feed water
- degassing system for removal of non-condensable gases (inert gases), the level of non-condensable gases (NCG) contained in the steam must have a level of not more than 3.5 % V/V, to attain sterilization conditions in any part of the sterilizer load
- thermic degassing system (buffer vessel, pre-heater, vacuum unit) for ozone degradation and degassing of NCGs
- water is evaporated, producing steam. The steam disengages from the water leaving behind pyrogens. Low molecular weight impurities are carried with the water as mist and/or droplets, which are entrained in the steam. Separator removes fine mist and entrains impurities.
- integrated natural circulation heat exchanger energy saving

NKG non-condensable gases

- NKG non-condensable gases are gases that do not condensate within the conditions of steam sterilisation. They stay gas as long as steam condensates to liquid water.
- It is the steam quality having a strong influence on sterilisation quality.
- Even very small ammounts of NKGs in steam (earlier called Intertgas), can harm reduction of germs to a non acceptable level. This is critical to the process.
- To guarantee a successfull sterilisation, air must be removed from the sterilisation chamber and material to be sterilised (by vacuum cycles).
- Success of sterilisation can NOT be guaranteed by longer hold times!
- Limits are:
  - Max. Level of NKG = max. 3,5 V/V%

Clean Steam Column – FAT check points / tests (example)

- Qualification of welder
- Visual quality inside / outside
- Documentation, Parts-List, Material-List
- PT-Test (red/white)
- Pressure Test
- Ra-Measurement (surface roughness)

Qualification of water systems

- But special PQ in 3 phases (FDA guide to inspection of high purity water systems)
- Report for each phase

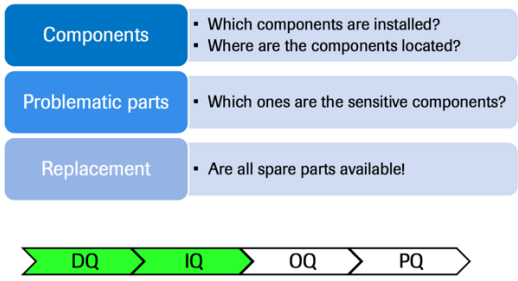
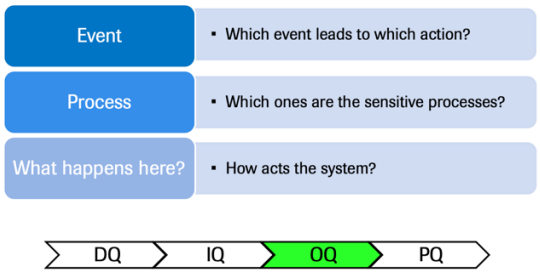
Phase	Sampling	Details
1	2-4 weeks Daily All points of use or sampling points	Setting up best parameters Setting alarm and warning limits Sop for use and maintenance
2	2-4 weeks Daily Alternating at all points of use or sampling points	Proof of quality
3	52 weeks Daily Alternating at all points of use or sampling points, minimum each point weekly	Long term proof of quality Seasonal differences Variability of feed water Variable use

PQ Phase – "System Validation"

"Validation often involves the use of an appropriate challenge. In this situation, it would be undesirable to introduce microorganisms into an on-line system; therefore, reliance is placed on periodic testing for microbiological quality and on the installation of monitoring equipment at specific checkpoints to ensure that the total system is operating properly and continuously fulfilling its intended function."

Validation documentation of a high purity water system:

- Description of the system along with a drawing that shows all equipment in the system from the water feed to points of use, all sampling points and their designations
- Drawing has to be compared to the actual system annually to insure its accuracy, to detect unreported changes and confirm reported changes to the system
- While the above validation scheme is not the only way a system can be validated, it contains the necessary elements for validation of a water system.
  - First, there must be data to support the SOPs.
  - Second, there must be data demonstrating that the SOPs are valid and that the system is capable of consistently producing water that meets the desired specifications.
  - Finally, there must be data to demonstrate that seasonal variations in the feedwater do not adversely affect the operation of the system or the water quality.
- The last part of the validation is the compilation of the data, with any conclusions into the final report. The final validation report must be signed by the appropriate people responsible for operation and quality assurance of the water system.

<table>
<tr><th>Details in installation</th><th>Process knowledge</th></tr>
<tr><td> 
</td><td> 
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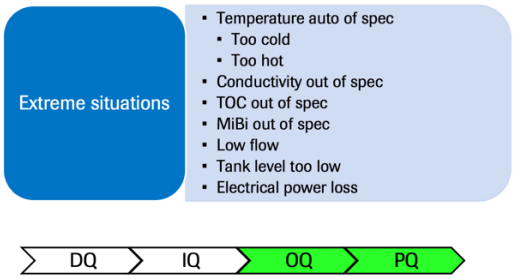
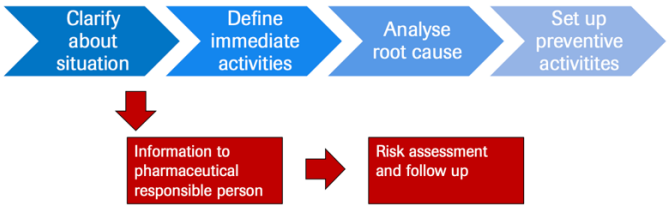
<tr><th>Acting in extreme situation</th><th>Acting in extreme Situation</th></tr>
<tr><td> 
</td><td> 
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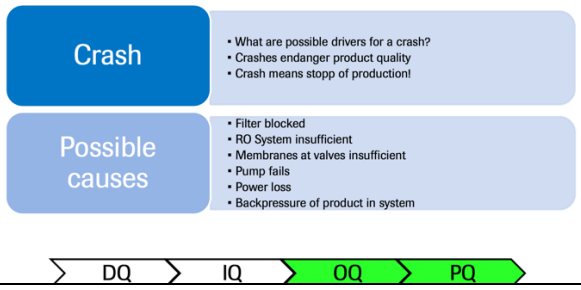
<tr><td>Avoid Crashes</td><td> 
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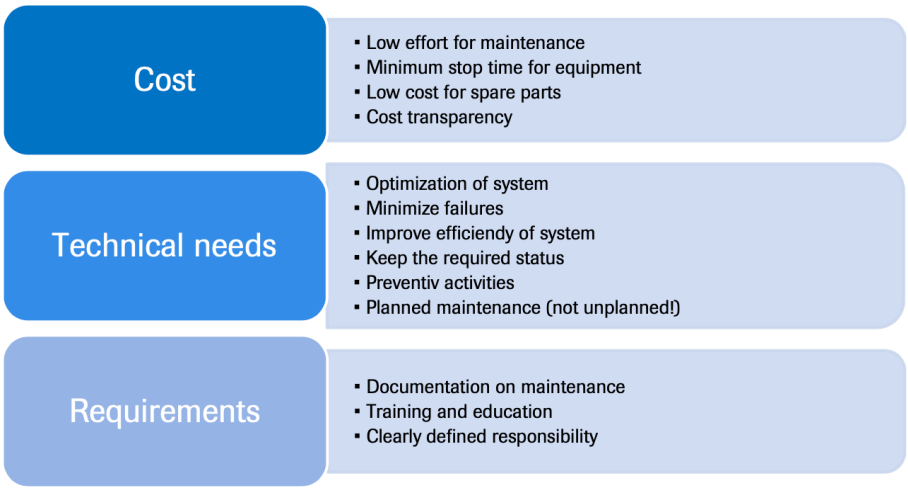
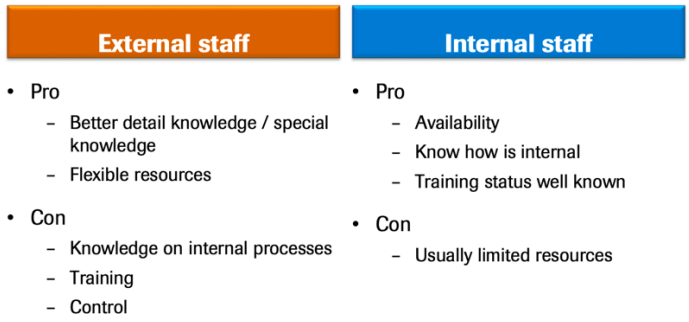
Maintenance – What is sufficient



- Definition of maintenance intervals
- Analyze membranes and sealings with a classification system
- Decide on this basis how often the have to be changed

Who should perform maintenance?



Maintenance – Summary

- Knowledge about a system is important to avoid problems and have quick response time on problems
- Maintenance is a tool to keep the qualified status up to date
- Monitoring is a tool to keep a system under control and enables you to act before problems occur
- Inspections and audits are no problem with a system that is under control!

Monitoring Program

A monitoring program that contains the procedures that describe the sampling and testing methods used to assure acceptable quality of the water system must be implemented for all water systems

Monitoring Plan/Sampling Pan

- A risk based approach must be employed to further define the specific sampling locations and frequencies
- Sampling program rationales must be established based on:
  - risk impact
  - system validation data
  - criticality of the processes for which the water is used
- Water systems must be monitored at a frequency that is sufficient to ensure that the system is in control and continues to produce water of acceptable quality
- Samples must be taken from representative locations within the distribution system

Chemical Cleaning and Sanitization

- Chemical cleaning and/or sanitization are used to keep scaling, fouling or biofouling proliferation under control
- Chemical cleaning and sanitization methods and frequencies must be based on system performance and planned responses to system downtimes, changes and excursions
- The use concentration of chemicals, exposure times and/or temperatures must be qualified and defined
- Periodic cleaning is normally used for membrane systems including the pretreatment and water plants that can not be sanitized with hot water

Chemical cleaning

- The cleaning conditions must be **suitable for** the system and the construction **materials**
- **Cleaning agents** must be **completely removed** from the system at the end of the cleaning procedure
- **Removal of cleaning agents must be confirmed** using analytical methods

Sanitization

- **Heat** penetration must **reach all moist surfaces** to prevent cold spots
- Water systems that are operated at **temperatures ≥ 70 °C** are regarded as **self-sanitizing** and need not be cleaned or sanitized separately
- Three types of sanitization may be applied:
  - **Hot water** sanitization: The whole water system is sanitized with hot water
  - **Pure steam** sanitization: Dependent on the construction materials, either the whole or part of the water system is sanitized with pure steam at temperatures ≥ 121 °C
  - **Ozone** may be used to keep bioburden under control. An efficient removal of ozone must be achieved prior to use of the water

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ASME BPE /ISPE Rouging Classification

- Class I: Migratory Rouge – consists of various oxides and hydroxides derived from source metals (iron oxide or ferrous oxide (FeO) being the most prevalent). It predominantly is orange to red-orange, is particulate in nature, and tends to migrate from its originating point on the original metal surfaces. The deposited particles can be removed from the surface leaving the composition of the stainless steel unchanged.
- Class II: In-Situ Oxidation of Non-Passive Surfaces – localized form of active corrosion (iron oxide or ferric oxide – hematite (Fe_2O_3) being the most prevalent). It occurs in a spectrum of colors (orange, red, blue, purple, grey, and black). It can most commonly be the result of chloride or other halide attack on the surface of the stainless steel. Integral with the surface, it appears more frequently on mechanically polished surfaces.
- Class III: Black Oxide Produced by Hot-Oxidation – surface oxidation condition occurring in high temperature environments, such as pure steam systems. As the rouge layer thickens, the system's color transitions from gold to blue and to various shades of black. This surface oxidation initiates as a stable film and is rarely particulate in nature. It is an extremely stable form of magnetite (iron sesquioxide (an oxide containing two atoms or radicals of some other substance), (Fe_3O_4)).

Purpose

- De-rouging and re-passivation operations were identified as a limiting factor to reduce shutdown durations and frequency.
- The overall goal is to reduce shutdowns for de-rouging/repassivation activities.
- A risk based approach is used for the classification and handling of rouging.
- General recommendations exist for classifying rouging, performing de-rouging and re- passivation, as well as potential preventative measures.
- According to cGMP guidelines, production equipment must be maintained in a condition that ensures safe production without any negative influence to the product. This includes:
  - Cleanability of production equipment
  - Prevention of adverse effects on product quality (e.g. contamination through rouging particles or heavy metal ions)

Regulatory Requirements

- At present, the subject of "rouging" is not directly mentioned in any regulatory requirement.
- Nevertheless, some regulations pertaining to stainless-steel surfaces and cleanability of equipment used for production contain references to rouging (see Table).
- The regulatory requirements listed in the Table are directed primarily at cleanliness and cleanability. What is required is prevention of risk to the product quality due to contamination with foreign matter originating from unsuitable and or inadequately cleaned production systems.

Recommendations based on Risk Analysis

- Cold / Ambient Water Systems: These systems are typically not affected by rouging since one of the major contributing factors for rouging (high temperature) is not present. Therefore, de-rouging and re-passivation of these systems is not necessary. Water from these systems is typically used as either feed- water for WFI, feed-water for Highly Purified Water generation, or is filtered prior to use to remove potential particles.
- Hot Water Systems: Hot water (WFI) generation and distribution systems are typically affected by orange to reddish deposits (Rouging Class I to II). Removal of this rouging type induces the risk of high particle count after cleaning for an extended time period (>3 months observed). Derouging / re-passivation of these systems is not recommended for DS assets. For DP assets, due to the risk of a particle contamination of product contacting surfaces especially in the final filling facilities, at minimum rouging deposits should be monitored, and de-rouging and re-passivation should be performed only if necessary.
- Clean Steam: Clean steam systems, including pure steam generators, can be affected by violet to black discolorations due to high temperatures (Rouging Class III). These types of discolorations are considered to be very stable; therefore the probability of particle release is very low and reoccurrence within a short time period is very high. Thus, de-rouging / repassivation of clean steam generation / distribution systems is not necessary for DS and DP assets.

Return to Service

- It must be ensured that all chemicals used for de-rouging / repassivation are fully removed from the treated equipment.
- This must be determined and documented (e.g. by measuring conductivity) in the final rinse steps after de-rouging / re-passivation operations.
- Like other maintenance activities, return to service procedures, including cleaning (CIP / SIP) after de-rouging / re-passivation of equipment, must be performed according to local procedures.

Meetings

- Regular meeting at construction area
- Meet craftsmen at their place
- Solve problems where they happen