PRODUCTION OF PW/HPW/WFI AND USP/EP REQUIREMENTS

Erez Eilam
F&U Area Lead
Novartis Singapore Bio production Operations

Agenda

- Background
- USP/EP Standard
- Steps in production
- Available technologies
- Key aspects in selection of a production system
- Possible production configurations

Background

- PW&WFI are the most common water source used for production in the pharmaceutical industry.
- During project implementation the water system has a great impact on the planning and schedule
- The specification of the water is quality critical, and other than the obvious routine implications, can impact the C&Q activities in a project
- Therefore when selecting a system, consideration for many factors must be made in order to provide a quality system with reliability and availability.
- With proper design, capital cost and operational cost can be reduced

USP/EP Standard

PW	USP	EP
Process	Distillation, Reverse Osmosis or other suitable process	Distillation, Ion Exchange, reverse osmosis or other suitable process
Conductivity	≤1.3μS/cm@25°C	≤4.3μS/cm@20°C
Bacteria [CFU]	<100/ml	<100/ml
Endotoxin	NA	<0.25 EU/ml (only for bulk water or dialysis)
TOC [ppb]	≤500	≤500
pH	5-7	5-7

USP/EP Standard

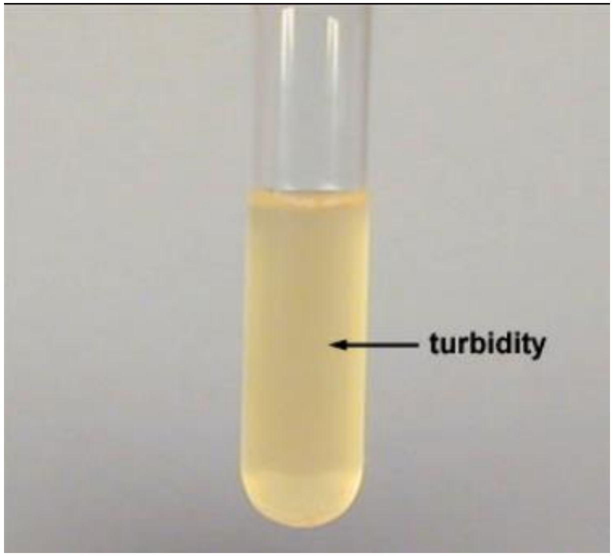
HPW	USP	EP
Process	NA	Double Pass RO coupled with other suitable final treatment (UF, EDI etc)
Conductivity	NA	≤1.1μS/cm@20°C
Bacteria [CFU]	NA	<10/100ml
Endotoxin	NA	<0.25 EU/ml
TOC [ppb]	NA	≤500
pH	NA	5-7

USP/EP Standard

WFI	USP	EP
Process	Distillation or Reverse Osmosis or equivalent	Distillation **Effective of APR 2017, alternative methods, such as RO are acceptable**
Conductivity	≤1.3μS/cm@25°C	≤1.1μS/cm@20°C
Bacteria [CFU]	<10/100ml	<10/100ml
Endotoxin	<0.25 EU/ml	<0.25 EU/ml
TOC [ppb]	≤500	≤500
pH	5-7	5-7

Steps in production
Removal of suspended solids/Turbidity

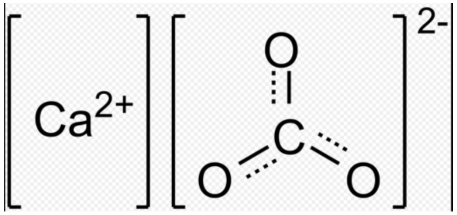
- Turbidity of the water can be identified visually and is caused by insoluble suspended and colloidal materials (such as dust, Pollen, Silica, corrosion products etc.)
- Particles are removed to avoid impact on other downstream processes such as overloading/blocking of resins, RO etc.
- Removing turbidity improves downstream processes and microbial control



Steps in production
Removal of Hardness

- Hardness is defined as the amount of Calcium and Magnesium in the water.
- In the final steps of purification, the concentration of di and tri valent cations (mostly Calcium and Magnesium) will tend to precipitate as calcium carbonate and magnesium carbonate and stick to downstream membranes, heat exchangers and other equipment.

$$Ca(OH)_2 + CO_2 \longrightarrow CaCO_3\downarrow + H_2O$$



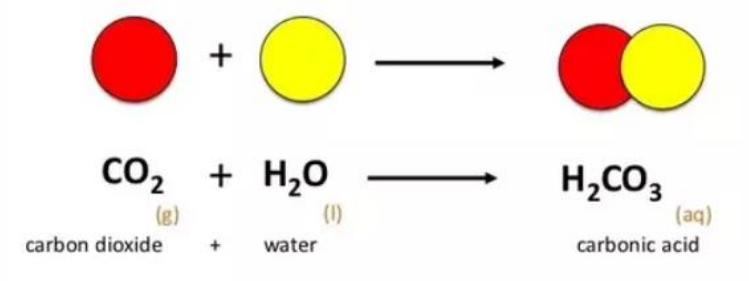
Steps in production

Microbial Control and Organic contaminants (TOC)

- Organic material can create load on the system and effect the efficiency of the process
- Bacterial growth also impacts the content of organic material in the system and will impact the key acceptance criteria (CFU, Endotoxin, TOC , Conductivity)
- Disinfection / Sanitization **is very critical** in the system design to avoid bacterial growth
- Added substances for the purpose of disinfection **may have to be removed** in order not to compromise steps downstream.

Steps in production
Removal of dissolved gases

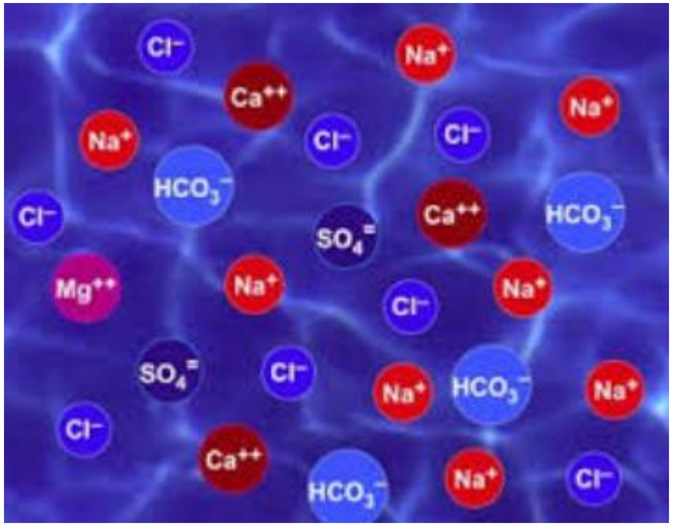
- CO2, Ammonia and other dissolved gases can pass directly though the RO membrane to the product stream and increase conductivity in the product
- High purity water naturally absorb CO2 from the air as it is equilibrium with carbonic acid in aqueous solutions



- CO2 can also be formed after acidification in upstream stages
- These dissolved gases also create load on the downstream process for ion removal
- In addition when using the product for clean steam production, there is impact on the quality of the clean steam as non condensable gases will impact sterilization efficiency

Steps in production
Reduction of conductivity

- Conductivity is a good indicator for contaminants which are dissolved ionized solids (calcium, phosphates, nitrates, sodium, potassium etc.)
- Conductivity is already reduced as part of the previous steps in the process, but In order to meet EP/USP requirements additional steps to remove the remaining ions and reduce conductivity to a minimum.



Available Technologies
Removal of suspended solids/Turbidity

Media Filtration:

- Single or multi media size filtration
- typically sand is the common filtration media
- Removal of particles 10-40µm
- Routine backwash required

Advantages:

- Low cost of operation
- Suited for typical city water feed (chlorinated)

Disadvantages:

- Can be a source for microbiological contamination without proper maintenance
- Floor space is required

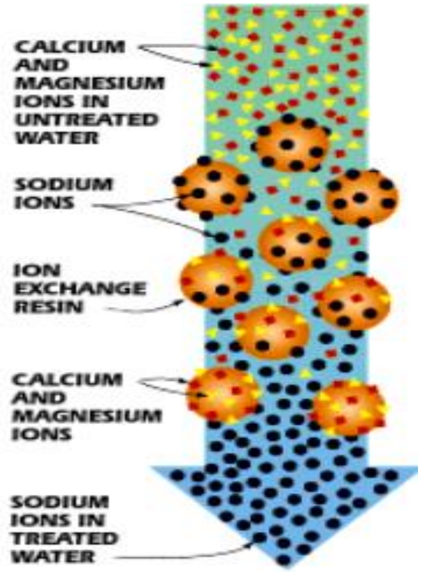
Available Technologies
Removal of Hardness

Ion Exchange:

- Softener column are charged with resin with affinity to positive ions, initially charged with sodium
- Water "softening" is achieved via exchanging of magnesium, calcium and similar cations with sodium

$$Ca^{++} + 2NaR \rightleftharpoons CaR_2 + 2Na^{+}$$

- Sodium ions are charged to the resin via NaCl dissolved in water
- Typically an additional softener column will be added to reduce down time during regeneration.



Available Technologies
Removal of Hardness

Advantages:

- Most common approach and considered to be robust and reliable

Disadvantages:

- Potential microbial growth
- Regeneration sequence requires routine top up of salt
- Sensitive to oxidizers such as chlorine
- Including Sanitization, backwash and regeneration times,

  down time could be considerable
- Floor space is considerable for softener columns and brine tank
- Needs to be replaced every 1-5 years
- Sodium and chlorides waste treatment

Available Technologies
Removal of Hardness

Additional processes :

Chemical dosing:

Acidification (typically with sulfuric acid) to lower the PH will convert carbonate to CO2 (gas), which can be removed later in the process.

Advantages:

- Less floor space is needed (drums for chemicals)
- No regeneration
- CO2 is released to the air , the sulfate ion from the acidification is easier to remove than the sodium ion in softening

Disadvantages:

- Fluctuations may impact the control and dosing
- Handling of acid and base solutions

$$CO_2\,(g) \rightleftharpoons \mathbf{CO_2}\,(aq)$$
$$CO_2\,(aq) + H_2O\,(l) \rightleftharpoons \mathbf{H_2CO_3}\,(aq)$$
$$H_2CO_3\,(aq) \rightleftharpoons \mathbf{HCO_3^-}\,(aq) + H^+\,(aq)$$
$$HCO_3^- \rightleftharpoons \mathbf{CO_3^{2-}}\,(aq) + H^+\,(aq)$$

Available Technologies
Removal of Hardness

<u>Electrolysis (In conjugation with RO)</u> :

- Precipitation is induced by electrolysis which increases the PH locally near the cylinder wall, this removes the scaling forming ions from the water
- The water are brought to a state where the kinetics of precipitation is slow
- The next step which is typically the RO will remove the scaling to the retntate

<u>Advantages:</u>

- No chemical additives or additional disinfection required
- Floor space is smaller compared to a softener skid
- No regeneration down times
- No extended sanitization periods
- Lower operational cost

<u>Disadvantages:</u>

- Can be impacted by water feed quality and flow variation
- Requires RO to function
- Does not produce soft water
- Capital cost is high

[Source: https://biopuremax.com]

Available Technologies
Microbial control – TOC reduction

Chlorine/ chloramine dosing:

- Typically done using Sodium Hypochlorite (NaOCL) at concentrations of 0.2-0.5ppm or chloramine (NH2CL), which in aqueous solutions will form hypochlorous acid - the most active moiety of the reaction:

$$NaOCl + H_2O \rightarrow HOCl + OH^-$$

$$NH_2Cl + H_2O \rightarrow HOCl + OH^-$$

- Although city water is chlorinated, re-chlorination and controlled dosing may be required during the process
- Consider vessels for mixing and control and reaction time

Advantages:

- Low cost
- Easy to test and control

Disadvantages:

- Attacks membranes, Resins, EDI and stainless steel
- Requires removal steps later in the process

Available Technologies
Microbial control – TOC reduction

Heating:

- Organisms are killed above 60°C and the majority of pathogenic organisms will not proliferate. Temperatures above 80°C will result in complete kill of all non-resistant bacteria
- Maintaining temperatures above 80 degC for 1-2 hours, when using ACF and softeners the entire process can take 4-8 hours
- Can be done via water heating or direct steam contact

Advantages:

- Well established and reliable
- No additional step is required to remove any additives

Disadvantages:

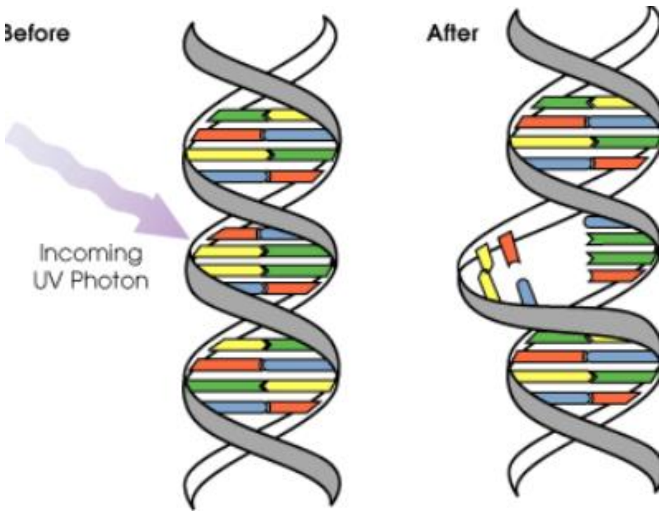
- High energy consumption
- Construction material will typically be from Stainless steel and increase the capital cost
- Down time for the system

Available Technologies
Microbial control – TOC reduction

Ultraviolet light:

- UV light at a wavelength of 240-280nm can attack bacteria at the DNA level (pyrimidine bases become reactive and bind covalently to each other) which prevents proliferation and ultimately kills bacteria.
- UV light at 185nm can produce highly reactive hydroxyl free radicals (short lived) , these free radicals will react rapidly with organic molecules (including bacteria) and create carboxylic acids which are ions that will increase conductivity in water, these ions can be removed in downstream steps
- Commercial medium pressure mercury vapor fluorescent light bulbs for this application emit UV at a wavelengths of 254nm and 185nm, the bulbs are installed in a chamber and the flow passes through it

[source: ISPE Baseline® Guide: Water and Steam Systems 13.5.1.1]



Available Technologies
Microbial control – TOC reduction

Ultraviolet light:

Advantages:

- Efficient when downstream processes are susceptible to chemicals
- No additional step is required to remove any additives

Disadvantages:

- Cannot operate with suspended solids , so ideally should be located right upstream of the RO
- Typically is not the only solution but is used as a part of an overall design (less efficient when there is rouging or biofilm)
- Additional filters downstream required for remaining bacteria
- Sensitive to fluctuations in flow and feed quality
- Preferably should be designed with a circulation loop

Available Technologies
Removal of Chlorine/Chloramine

Carbon:

- Activated carbon is the most common method for the removal of chlorine as well as organic material by adsorption
- Adsorption of chloramines is weaker than chlorine
- Absence of chlorine should be verified with ORP sensor
- Requires backwashing and sanitization

Advantages:

- Robust, not sensitive to fluctuations in concentration and flow

Disadvantages:

- High potential for microbial growth
- Requires sanitization with heat (either heated water or steam)
- Additional filter downstream is required in case of fine particles breaking up
- Periodic replacement of the carbon bed is required
- Floor space to be considered

Available Technologies
Removal of Chlorine/Chloramine

Sulfite Reduction (SBS) :

Dosing of sodium bi sulfite can reduce chlorine to chloride ions and chloramine to ammonium and chlroide ions which can be removed by the RO membrane

Advantages:

$$NaHSO_3 + CL_2 + H_2O \longrightarrow NaHSO_4 + 2HCl$$

- Low cost
- Less floor space (a chemical drum)

Disadvantages:

- Difficult to optimize
- If dosing is excessive, SBS can buildup on the membrane

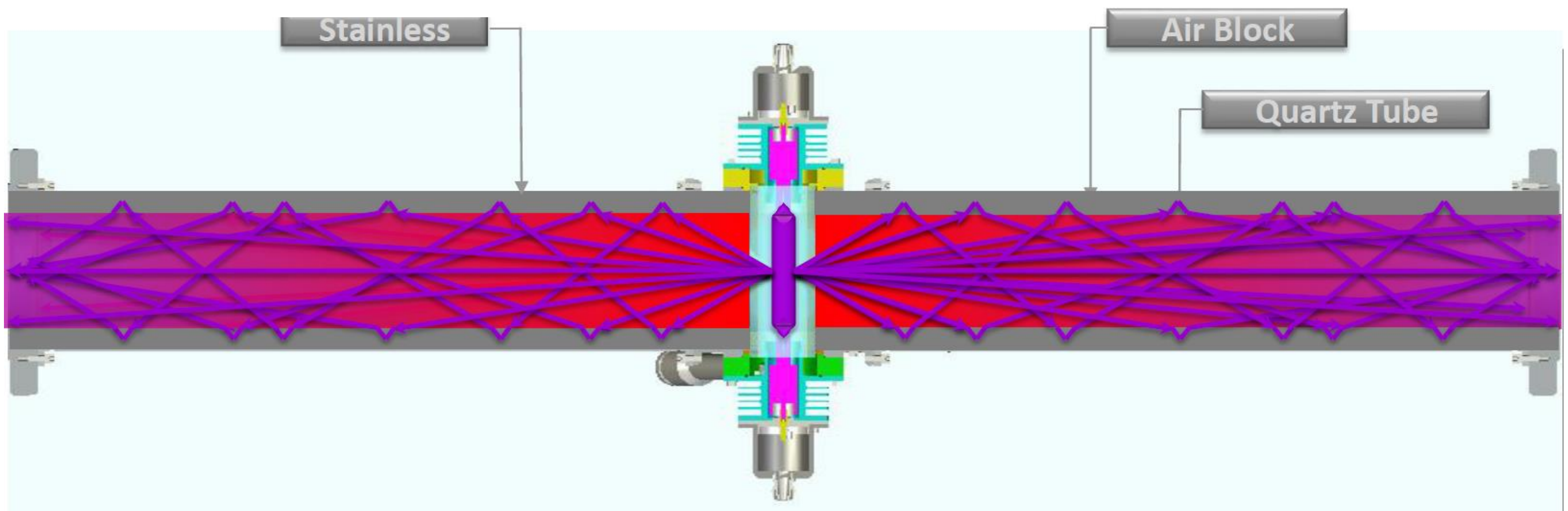
Available Technologies
Removal of Chlorine/Chloramine

UV light :

- UV can break the chemical bonds of chlorine and chloramine to form hydrochloric acid and other byproducts , which can be removed easily downstream at the RO.
- Requires about 20-30 times the dose compared to disinfection UV

$$2HOCl \rightarrow 2HCl + O_2$$

$$2NH_2Cl + HOCl \rightarrow N_2 + 3HCl + H_2O$$



[source: Biopuremax presentation, “Ro Pretreatment media and chemical free”, September 2017]

Available Technologies
Removal of Chlorine/Chloramine

Advantages:

- Small floor space compared to ACF
- No dosing of chemicals
- Compared to ACF sanitization is simple
- Low maintenance cost (lamp replacement)
- Reduced Bio fouling on RO compared to other methods

Disadvantages:

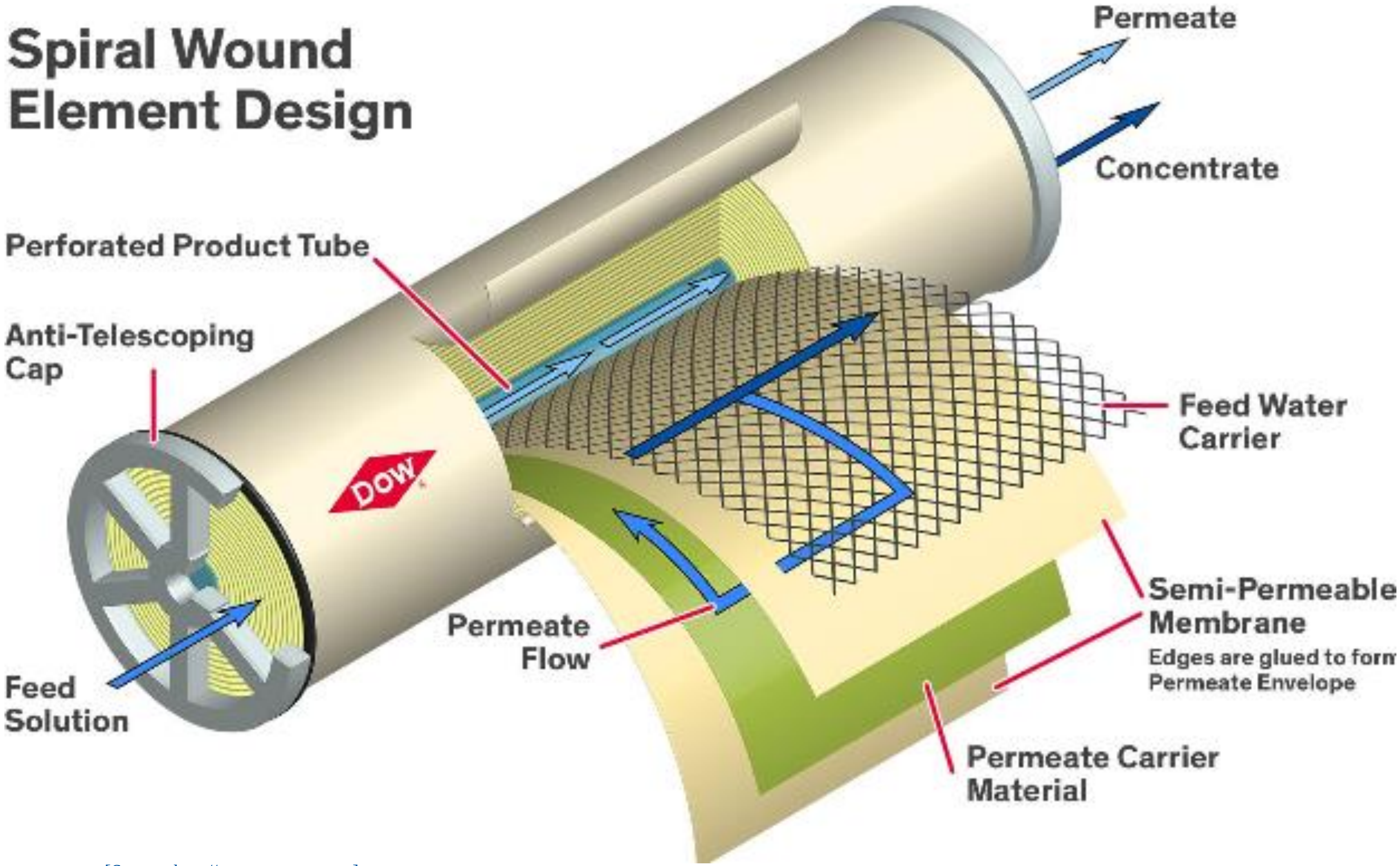
- Sizing depends on flows and concentration
- Less tolerance for variations in flow

Available Technologies
Reverse Osmosis

Reverse osmosis is the most common technology for water purification , water is pumped through a membrane at sufficient pressure .

- Pressure driven separation via semi permeable membrane
- The permeate is the purified water and the retentate is the concentrated stream which goes to drain
- The retentate can be recirculated to increase the recovery and reduce the waste stream (depending on factors recovery can reach 90%) [source: ISPE Baseline® Guide: Water and Steam Systems 5.1.1.2]

Available Technologies
Reverse Osmosis



[Source: http://www.evoqua.com]

Available Technologies
Reverse Osmosis

- RO+ CEDI + UF / Double Pass RO + CEDI / Double Pass RO + UF can meet HPW per EP (ISPE Baseline® Guide: Water and Steam Systems 5.1.1.2,)
- RO coupled with appropriate techniques can meet WFI requirements.

Advantages:

- Pore size up to 0.1nm, can remove organic and inorganic materials
- Reduces conductivity

Disadvantages:

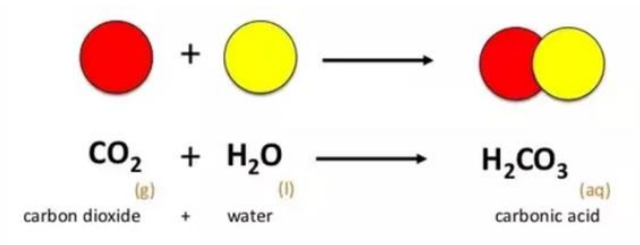
- Sensitive to chlorine and oxidation
- Requires routine maintenance and sanitization
- Temperature variation can increase permeate flow and reduce water quality
- Operating costs: pumping and heating and cooling

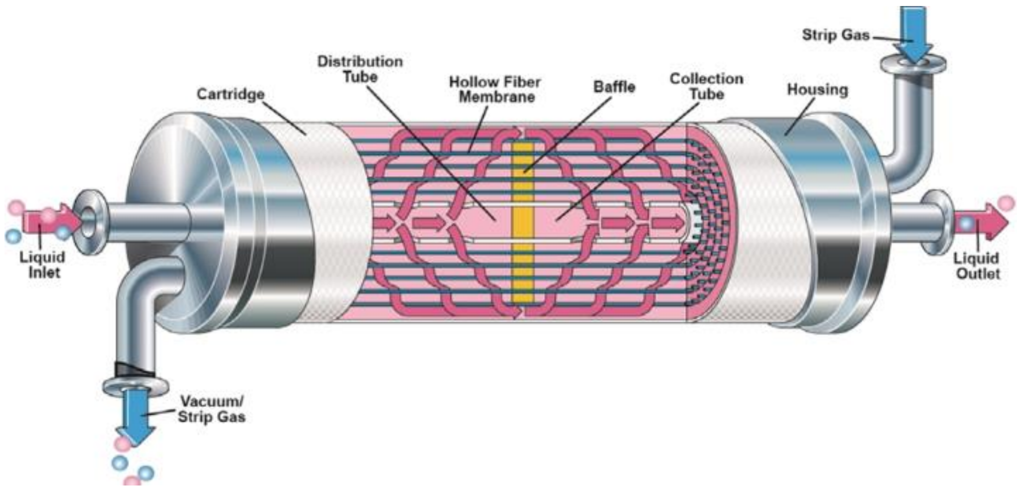
Available Technologies

Removal of dissolved gases

Degasification membrane

- Semi permeable membrane is used to allow only CO2 molecules to penetrate and be carried with the air to the air
- Since CO2 is in equilibrium with carbonic acid in the water, the evacuation of CO2 gas will shift the equilibrium to remove the carbonic acid as well
- Can reduce CO2 to levels below 5 ppm [source: ISPE Baseline® Guide: Water and Steam Systems 4.6.3]



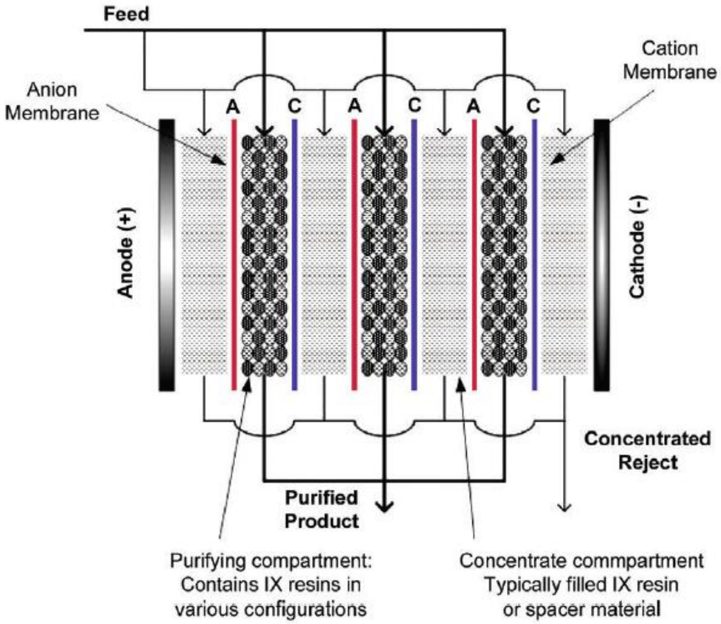


Available Technologies
Reduction of conductivity

CEDI – Continuous Electrical De Ionization

Combining ion exchange resins with selective membranes, in a continuous process

How does CEDI work



Available Technologies
Reduction of conductivity

CEDI – Continuous Electrical De Ionization

<u>Advantages:</u>

- Commonly used downstream of the RO membranes to
- No chemicals required
- Can reduce down to 0.1µS/cm

<u>Disadvantages:</u>

- Susceptible to chlorine
- Some models are susceptible to heat

Available Technologies
Single Effect Distillation

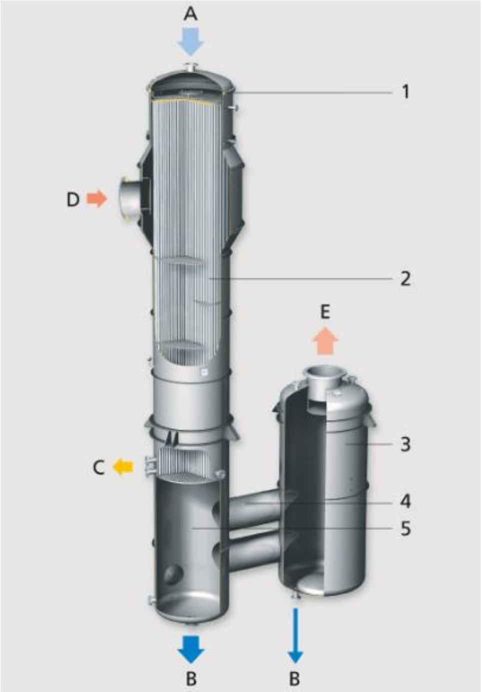
- Basic concept includes an evaporator, separation unit and a condenser based on falling film or rising film concept
- Black steam/electricity are required for heating , cooling media is required for the condenser
- Typically used for small plants where the WFI consumption low or infrequent.

Advantages:

- Low capital cost
- Lowest floor space for a distillation unit
- Can produce pure steam as well (with some design considerations)

Disadvantages:

- Operational costs are high
- Sensitive to stress corrosion and feed water quality



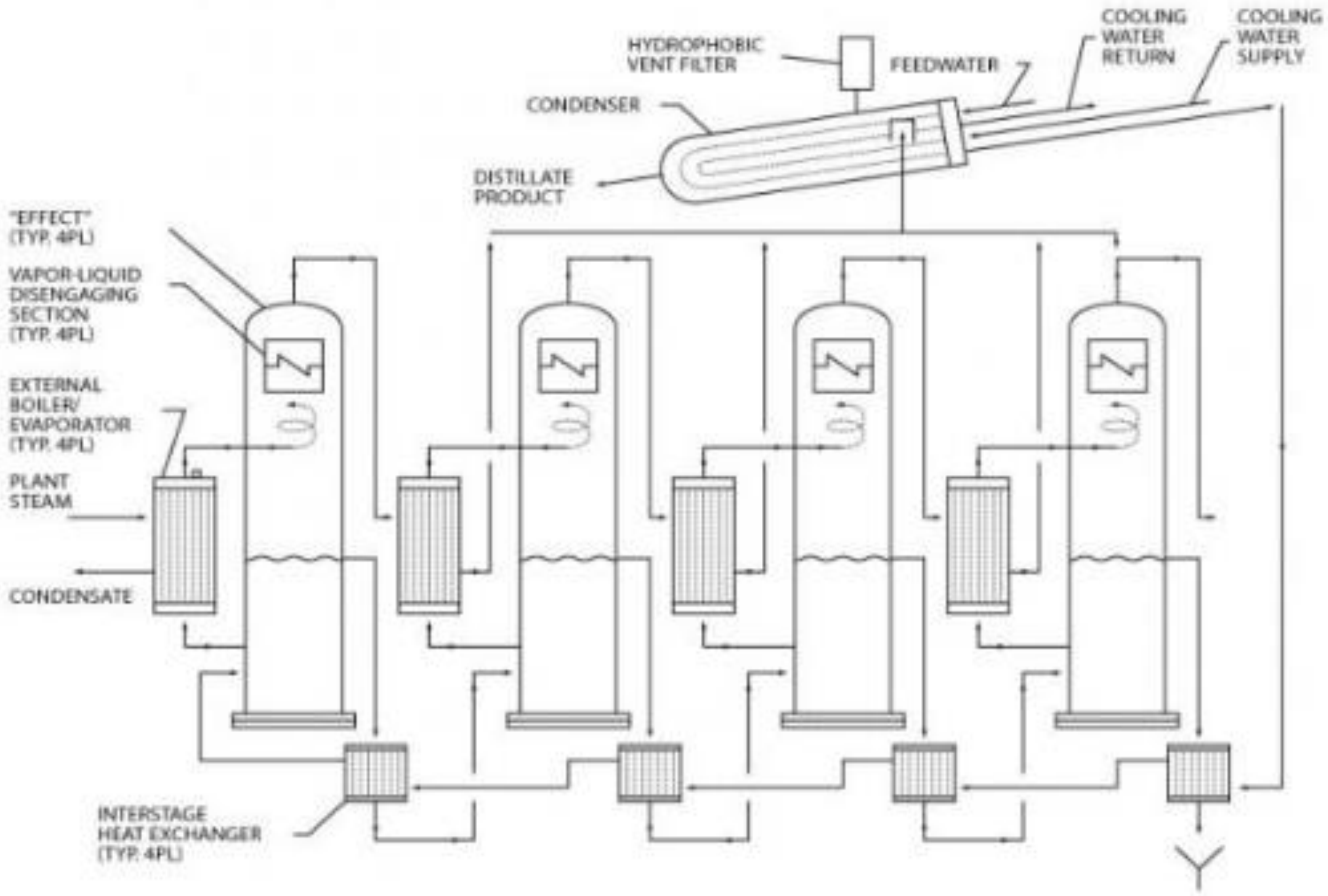
[Source: https://www.gea.com/en/products/falling-film-evaporator.jsp]

Available Technologies
Multiple Effect Distillation

- The first column uses “external” heat source (black steam/electricity) to heat the feed water and produce pure steam.
- Each effect produces pure steam which is used for heating in the subsequent effect
- The first column can also produce pure steam for the plant (with some design considerations)
- To produce WFI the Vapor from the final effect is condensed using “external”

  cooling (Chilled Water/cooling tower).

Available Technologies
Multiple Effect Distillation



[Source: http://www.ivtnetwork.com/gallery/water-systems-images]

Available Technologies
Multiple Effect Distillation

Advantages:

- Reduces the cooling and heating consumption
- Saves energy and operational cost
- Can also produce pure steam from the first column (potentially can save a pure steam unit)

Disadvantages:

- Sensitive to stress corrosion
- Requires feed quality
- WFI output pressure is atmospheric – slope constraints
- Feed pressure must be higher than the clean steam pressure (pump/ loop may be required)

Available Technologies
Vapor Compressor

- The water feed is heated and vaporized through the tubes in a tube bundle
- A compressor "sucks" the vapor and condenses it back on the outer surface of the tubes vapor to WFI
- Due to the compression the evaporation temperatures is lower than ME distillers
- The production capacity is proportional to the compressor speed
- The physical limit to the capacity is the heat transfer area and efficiency via the tubes

How does VC work

Available Technologies
Vapor Compressor

Advantages:

- Due to operation at lower temperatures and typically larger diameter pipes there is less stringent criteria for feed water
- Does not require cooling
- WFI production cost is lower

Disadvantages:

- If chloramine is present in the city water, removal of ammonia is required in order not to compromise the conductivity
- Will take more floor space compared to ME distiller
- More maintenance required due to moving parts
- Higher capital cost

Key Aspects in Selection of a Production System

User Requirements:

- Do all users require WFI or is also PW required?
- Is there requirement for pure steam as well?
- Existing/available utilities in the plant
- Floor space constraints

Cost:

- Capital cost
- Considering the entire steps of the system and not a single skid
- Considering construction material (SS/PVC)
- Operating cost – utilities, maintenance, consumables
- Sampling – PQ and routine, frequency

Key Aspects in Selection of a Production System

Availability:

- Calibration and impact on down time
- Maintenance (routine sanitization/backwash/ regeneration, topping up of chemical, replcaing filters and membranes)
- Redundancy

Waste:

- Brine
- Chemicals

Key Aspects in Selection of a Production System
Latest updates in EU

Until recently EP WFI could not be produced without distillation however HPW with the same specifications could be produced using RO e.g :RO+ CEDI + UF, Double Pass RO + CEDI and Double Pass RO + UF [source: ISPE Baseline® Guide: Water and Steam Systems 5.1.1.2]

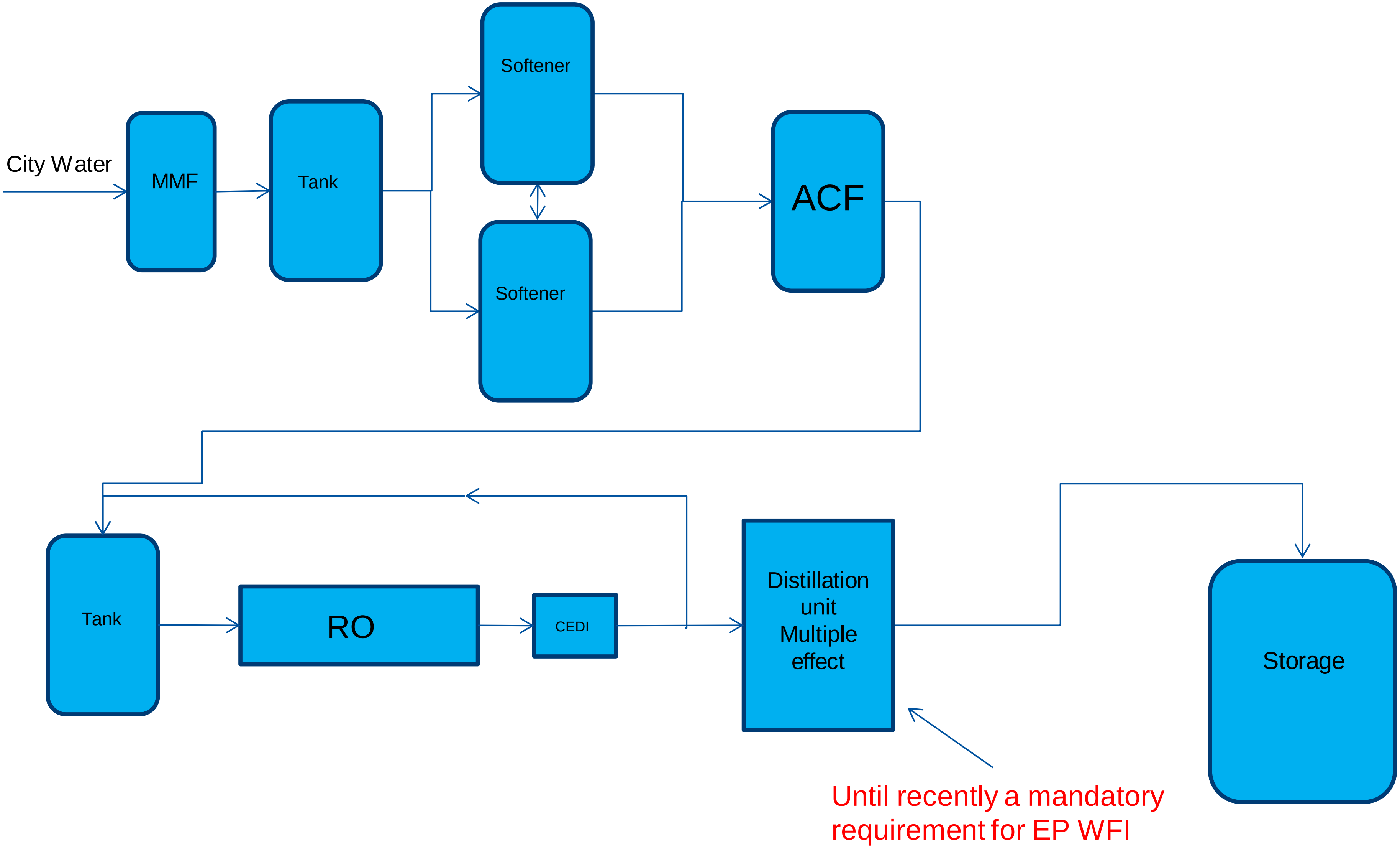
The latest monograph for *water for injections* (0169) was revised and published in Ph. Eur *supplement 9.1 (effective APR2017)* stating RO coupled with appropriate techniques can meet WFI requirements.

Additional appropriate techniques to be considered:

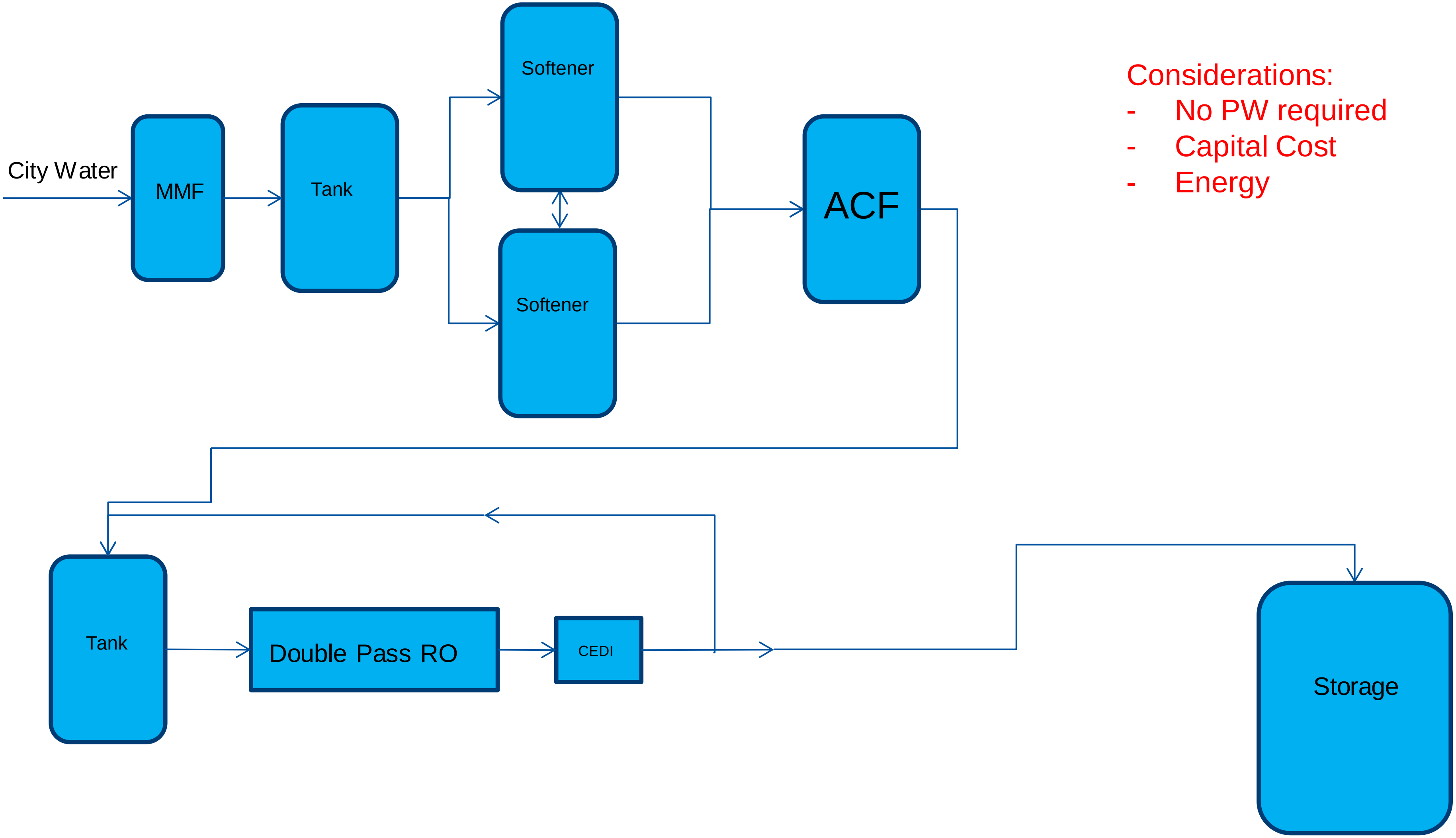
- Further techniques post RO membrane should be considered such as ultra-filtration (known to have an endotoxin reducing capability).
- Use of Double pass RO membranes should be considered as an added assurance of the maintenance of the quality of the water produced.
- Nano filtration, electro-deionization and ultra-filtration.
- Microfiltration (MF)/Ultrafiltration (UF) offers advantages in that it can remove microorganisms, which are sometimes very difficult to remove by standard techniques. The MF/UF membranes should be made from a chlorine-resistant material designed to allow for routine thermal and chemical sanitization and flushing.

[source: Questions and answers on production of water for injections by non-distillation 2 methods –reverse osmosis and biofilms and control strategies EMA/INS/GMP/443117/2017]

Possible Production Configurations

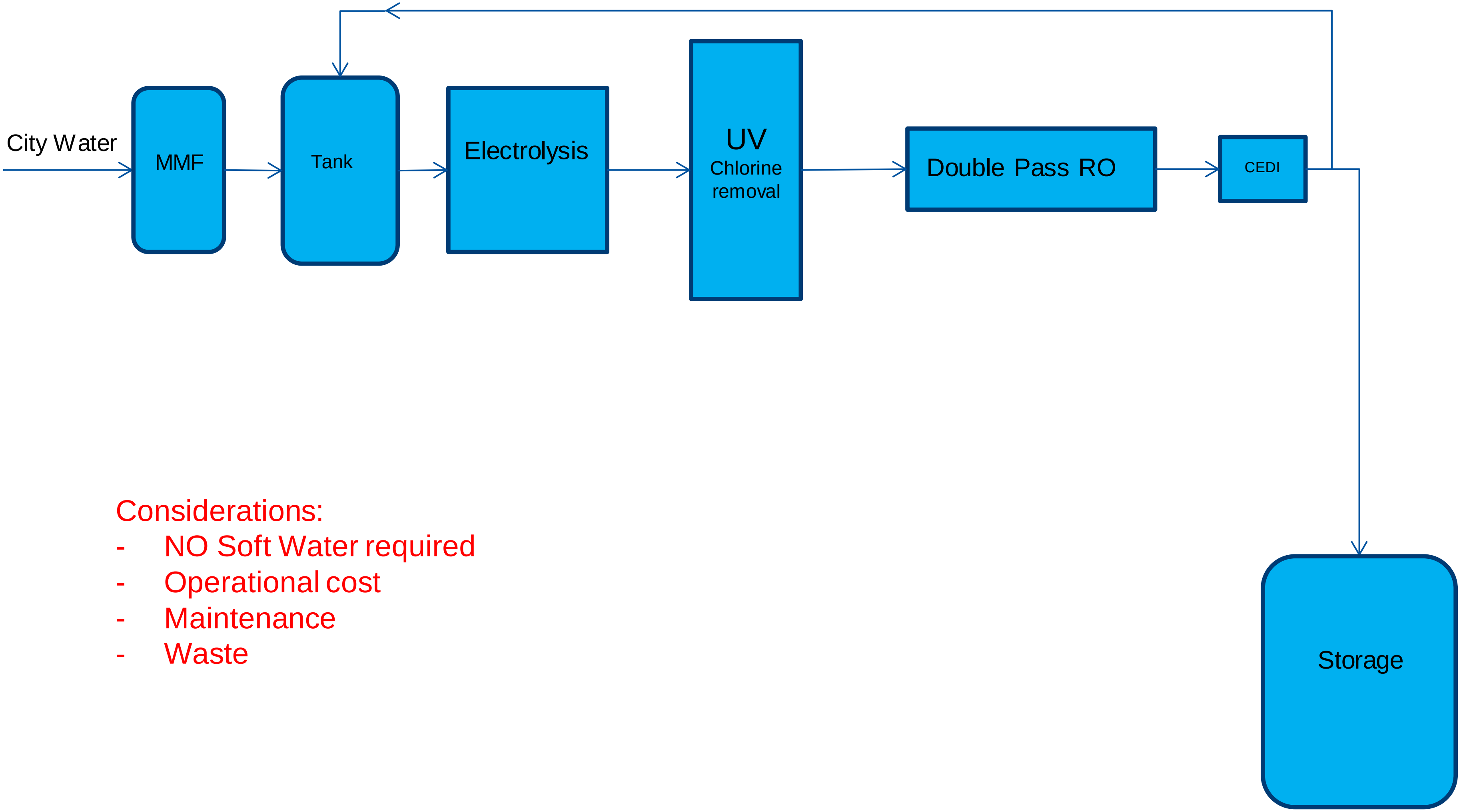


Possible Production Configurations



Considerations:
- No PW required
- Capital Cost
- Energy

Possible Production Configurations



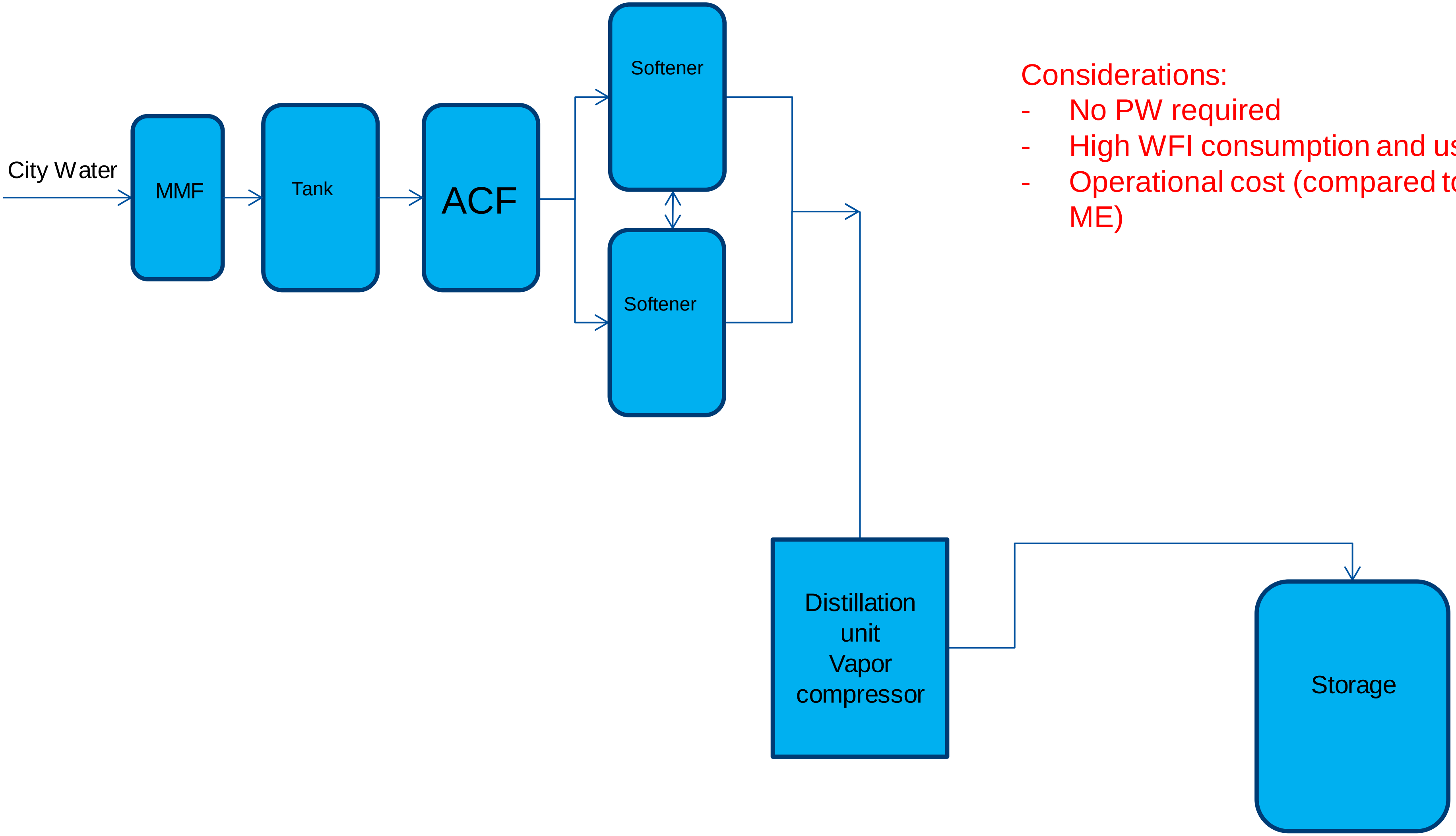
Considerations:

- NO Soft Water required
- Operational cost
- Maintenance
- Waste

Possible Production Configurations
Floor space

[Source: Biopuremax commercial brochure]

Possible Production Configurations



Considerations:
- No PW required
- High WFI consumption and use
- Operational cost (compared to ME)

Summary

- Production of PW and WFI has many implications on the plant during project and routine phase.
- The latest updates in the EP monograph allow for more flexibility and provides more options for configurations without distillation to produce WFI.
- When selecting a production system many factors must be considered such as : User requirements, Availability and Down time , Reliability Capital Cost, Operational cost , Waste management etc.